```
=> b hcaplus
FILE 'HCAPLUS' ENTERED AT 14:15:42 ON 10 OCT 2002
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FILE COVERS 1907 - 10 Oct 2002  VOL 137 ISS 15
FILE LAST UPDATED: 9 Oct 2002  (20021009/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

CAS roles have been modified effective December 16, 2001. Please
check your SDI profiles to see if they need to be revised. For
information on CAS roles, enter HELP ROLES at an arrow prompt or use
the CAS Roles thesaurus (/RL field) in this file.

=> d que l18
L1         13576 SEA FILE=HCAPLUS ABB=ON  PLU=ON  BIOAVAILABILITY+NT/CT
L2             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  L-ARGININE/CN
L3             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  NADPH/CN
L4             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  TETRAHYDROBIOPTERIN/CN
L6           862 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ECNOS OR ENDOTHELIAL NO
                 SYNTHASE
L7             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "NITROGEN MONOXIDE"/CN
L8         85771 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L7 OR NITRIC OXIDE OR
                 NITROGEN MONOXIDE
L10       218640 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8 OR NO(3A)INCREAS?
L11          818 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L10 AND L6
L12            4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L11 AND L1
L13           34 SEA FILE=HCAPLUS ABB=ON  PLU=ON  CEREB?(5A)BIOAVAIL?
L14            1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L11 AND L13
L15            4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L12 OR L14
L16           51 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L2 OR L3 OR L4) AND L1
L17            2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L16 AND (L6 OR L10)
L18            4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L15 OR L17


=> b medline
FILE 'MEDLINE' ENTERED AT 14:15:52 ON 10 OCT 2002

 FILE LAST UPDATED: 10 OCT 2002 (20021010/UP).  FILE COVERS 1958 TO DATE.

 On June 9, 2002, MEDLINE was reloaded.  See HELP RLOAD for details.
```

MÉDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2002 vocabulary. Enter HELP THESAURUS for details.

THIS FILE CONTAINS CAS REGISTRY NUMBERS FOR EASY AND ACCURATE SUBSTANCE IDENTIFICATION.

```
=> d que l26
L19        16373 SEA FILE=MEDLINE ABB=ON  PLU=ON  "BIOLOGICAL AVAILABILITY"/CT
L20        40807 SEA FILE=MEDLINE ABB=ON  PLU=ON  ENDOTHELIAL NO SYNTHASE OR
                 NO(3A)INCREAS? OR ECNOS
L21        30261 SEA FILE=MEDLINE ABB=ON  PLU=ON  NITRIC OXIDE/CT
L22         1926 SEA FILE=MEDLINE ABB=ON  PLU=ON  "NITRIC OXIDE DONORS"/CT
L25          135 SEA FILE=MEDLINE ABB=ON  PLU=ON  L19 AND (L21 OR L22 OR L20 OR
                 NITRIC OXIDE OR NITROGEN MONOXIDE)
L26            8 SEA FILE=MEDLINE ABB=ON  PLU=ON  L25 AND (BRAIN? OR CEREBR?)


=> d que l28
L19        16373 SEA FILE=MEDLINE ABB=ON  PLU=ON  "BIOLOGICAL AVAILABILITY"/CT
L20        40807 SEA FILE=MEDLINE ABB=ON  PLU=ON  ENDOTHELIAL NO SYNTHASE OR
                 NO(3A)INCREAS? OR ECNOS
L21        30261 SEA FILE=MEDLINE ABB=ON  PLU=ON  NITRIC OXIDE/CT
L22         1926 SEA FILE=MEDLINE ABB=ON  PLU=ON  "NITRIC OXIDE DONORS"/CT
L23        23754 SEA FILE=MEDLINE ABB=ON  PLU=ON  ARGININE/CT
L24        14458 SEA FILE=MEDLINE ABB=ON  PLU=ON  NADP/CT
L25          135 SEA FILE=MEDLINE ABB=ON  PLU=ON  L19 AND (L21 OR L22 OR L20 OR
                 NITRIC OXIDE OR NITROGEN MONOXIDE)
L27           26 SEA FILE=MEDLINE ABB=ON  PLU=ON  L25 AND ((L23 OR L24) OR
                 ARGININE OR NADPH OR TETRAHYDROBIOPTERIN)
L28           12 SEA FILE=MEDLINE ABB=ON  PLU=ON  L27 AND INCREAS?(8A)(NO OR
                 NITRIC OXIDE OR NITROGEN MONOXIDE OR BIOAVAIL? OR BIOLOG?(3A)AV
                 AIL?)


=> s l26 or l28
L53           19 L26 OR L28

=> b embase
FILE 'EMBASE' ENTERED AT 14:16:16 ON 10 OCT 2002
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 FILE COVERS 1974 TO 3 Oct 2002 (20021003/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d que l43
L29        15881 SEA FILE=EMBASE ABB=ON  PLU=ON  BIOAVAILABILITY/CT
L30        11287 SEA FILE=EMBASE ABB=ON  PLU=ON  "DRUG BIOAVAILABILITY"/CT
L31        35271 SEA FILE=EMBASE ABB=ON  PLU=ON  "NITRIC OXIDE"/CT
L33          106 SEA FILE=EMBASE ABB=ON  PLU=ON  ((L29 OR L30) AND L31)
L34        18906 SEA FILE=EMBASE ABB=ON  PLU=ON  ARGININE/CT
L35         5956 SEA FILE=EMBASE ABB=ON  PLU=ON  "REDUCED NICOTINAMIDE ADENINE
                 DINUCLEOTIDE PHOSPHATE"/CT
L36         1341 SEA FILE=EMBASE ABB=ON  PLU=ON  TETRAHYDROBIOPTERIN/CT
```

```
L37          37 SEA FILE=EMBASE ABB=ON  PLU=ON  L33 AND ((L34 OR L35 OR L36)
                OR ARGININE OR NADPH OR TETRAHYDROBIOPTERIN)
L40         717 SEA FILE=EMBASE ABB=ON  PLU=ON  ENDOTHELIAL NO SYNTHASE OR
                ECNOS
L41           4 SEA FILE=EMBASE ABB=ON  PLU=ON  L37 AND L40
L42           1 SEA FILE=EMBASE ABB=ON  PLU=ON  L37 AND (BRAIN OR CEREBR?)
L43           4 SEA FILE=EMBASE ABB=ON  PLU=ON  L41 OR L42


=> b drugu wpix
FILE 'DRUGU' ENTERED AT 14:16:30 ON 10 OCT 2002
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FILE 'WPIX' ENTERED AT 14:16:30 ON 10 OCT 2002
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=> d que l52
L45       40523 SEA BIOAVAIL? OR BIOLOG?(W) AVAIL?
L46       32712 SEA (NO OR NITROGEN MONOXIDE OR NITRIC OXIDE)(5A) INCREAS?
L47       17564 SEA ARGININE OR NADPH OR TETRAHYDROBIOPTERIN
L48         138 SEA ENDOTHELIAL NO SYNTHASE OR ECNOS
L49      107803 SEA BRAIN OR CEREBR?
L50         747 SEA L45 AND L46
L51          29 SEA L50 AND L47
L52           3 SEA L51 AND (L48 OR L49)


=> dup rem l53 l18 l52 l43
FILE 'MEDLINE' ENTERED AT 14:16:58 ON 10 OCT 2002

FILE 'HCAPLUS' ENTERED AT 14:16:58 ON 10 OCT 2002
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FILE 'WPIX' ENTERED AT 14:16:58 ON 10 OCT 2002
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FILE 'EMBASE' ENTERED AT 14:16:58 ON 10 OCT 2002
COPYRIGHT (C) 2002 Elsevier Science B.V.  All rights reserved.
PROCESSING COMPLETED FOR L53
PROCESSING COMPLETED FOR L18
PROCESSING COMPLETED FOR L52
PROCESSING COMPLETED FOR L43
L54          29 DUP REM L53 L18 L52 L43 (1 DUPLICATE REMOVED)

=> d ibib ab hitind 1-29

L54  ANSWER 1 OF 29     MEDLINE
ACCESSION NUMBER:   2002092383     MEDLINE
DOCUMENT NUMBER:    21679565   PubMed ID: 11821713
TITLE:              Irbesartan lowers superoxide levels and increases
                    nitric oxide bioavailability in
                    blood vessels from spontaneously hypertensive stroke-prone
```

rats.

AUTHOR: Brosnan M Julia; Hamilton Carlene A; Graham Delyth; Lygate Craig A; Jardine Emma; Dominiczak Anna F
CORPORATE SOURCE: BHF Blood Pressure Group, University of Glasgow, Department of Medicine and Therapeutics, Western Infirmary, Glasgow, UK.. mjb8n@clinmed.gla.ac.uk
SOURCE: JOURNAL OF HYPERTENSION, (2002 Feb) 20 (2) 281-6.
Journal code: 8306882. ISSN: 0263-6352.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020201
Last Updated on STN: 20020502
Entered Medline: 20020501

AB OBJECTIVE : To determine the effects of the angiotensin II receptor antagonist irbesartan, the calcium-channel blocker amlodipine, and hydrochlorothiazide/hydralazine on superoxide, NAD(P)H oxidase and **nitric oxide** bioavailability in spontaneously hypertensive stroke-prone rats (SHRSP). METHODS : Drugs or vehicle were administered for 8 weeks to SHRSP and blood pressure was measured weekly by tail-cuff plethysmography. After 8 weeks, superoxide levels in carotid arteries and aortas were measured by lucigenin chemiluminescence and p22phox expression quantified by immunohistochemistry. In vitro the effects of exposure to drugs and vehicle for 30 min and 4 h on superoxide levels and **nitric oxide bioavailability** were examined. The latter was expressed as the **increase** in contractile responses of carotid arteries to phenylephrine in the presence of the **nitric oxide** synthase inhibitor NG-nitro-l-**arginine** methyl ester(l-NAME). RESULTS : In vivo irbesartan, amlodipine and hydrochlorothiazide/hydralazine produced similar falls in blood pressure, from 162 +/- 4 to 125 +/- 5, 132 +/- 4 and 131 +/- 6 mmHg, respectively, but irbesartan caused a greater reduction in superoxide and p22phox; superoxide levels in carotid arteries being 3.1 +/- 0.3, 1.1 +/- 0.2, 1.9 +/- 0.3 and 2.0 +/- 0.3 nmoles/mg per min, respectively. In vitro 4 h exposure to irbesartan decreased superoxide levels in the aorta from 2.08 +/- 0.68 to 1.48 +/- 0.62 nmoles/mg per min and **increased nitric oxide bioavailability** in carotid arteries. Neither 30 min incubation with irbesartan nor 4 h with amlodipine or hydrochlorothiazide/hydralazine altered superoxide levels. CONCLUSIONS : These studies support the hypothesis that AT1 receptor blockade has beneficial effects on superoxide production and **nitric oxide** bioavailability above that of other classes of antihypertensive agents. Reduced expression of components of the NAD(P)H oxidase may contribute to these effects.

CT Check Tags: Animal; Comparative Study; Female; Male
Amlodipine: PK, pharmacokinetics
Amlodipine: TU, therapeutic use
Angiotensin II: PD, pharmacology
*Antihypertensive Agents: PK, pharmacokinetics
*Antihypertensive Agents: TU, therapeutic use
Aorta: CH, chemistry
Aorta: DE, drug effects
Biological Availability
*Biphenyl Compounds: PD, pharmacology
*Biphenyl Compounds: TU, therapeutic use

Blood Pressure: DE, drug effects
*Blood Vessels: DE, drug effects
*Blood Vessels: ME, metabolism
Cerebrovascular Accident: CO, complications
Cerebrovascular Accident: DT, drug therapy
Disease Models, Animal
Drug Therapy, Combination
Hypertension: CO, complications
Hypertension: DT, drug therapy
Immunohistochemistry
NADPH Dehydrogenase: DE, drug effects
NADPH Dehydrogenase: PH, physiology
***Nitric Oxide: PK, pharmacokinetics**
Phosphoproteins: DE, drug effects
Phosphoproteins: PH, physiology
Rats
Rats, Inbred SHR
*Receptors, Angiotensin: AI, antagonists & inhibitors
*Receptors, Angiotensin: PH, physiology
Receptors, Angiotensin: TU, therapeutic use
*Superoxides: ME, metabolism
*Tetrazoles: PD, pharmacology
*Tetrazoles: TU, therapeutic use

RN **10102-43-9 (Nitric Oxide)**; 11062-77-4 (Superoxides); 11128-99-7 (Angiotensin II); 138402-11-6 (irbesartan); 88150-42-9 (Amlodipine)

CN 0 (Antihypertensive Agents); 0 (Biphenyl Compounds); 0 (Phosphoproteins); 0 (Receptors, Angiotensin); 0 (Tetrazoles); 0 (p22-phox); EC 1.6.99.1 (**NADPH** Dehydrogenase)

L54 ANSWER 2 OF 29 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2002142937 EMBASE
TITLE: Physiology of folic acid in health and disease.
AUTHOR: Stanger O.
CORPORATE SOURCE: O. Stanger, Karl-Franzens Univ. School of Med., Department of Surgery, Division of Cardiac Surgery, Auenbruggerplatz 29, A-8036 Graz, Austria. o.stanger@lks.at
SOURCE: Current Drug Metabolism, (2002) 3/2 (211-223).
Refs: 150
ISSN: 1389-2002 CODEN: CDMUBU
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Folates are important cofactors in the transfer and utilization of one-carbon-groups and play a key role in the remethylation of methionine thus providing essential methyl groups for numerous biological reactions. Furthermore, folates donate one-carbon units in the process of DNA-biosynthesis with implications for the regulation of gene expression, transcription, chromatine structure, genomic repair and genomic stability. As the role of folate deficiency in atherosclerotic cardiovascular disease, neurological and neuropsychiatric disorders, in congenital defects and carcinogenesis has become better understood, folate has been recognized as having great potential to prevent these many disorders through folate supplementation for the general population. Folate acts

directly to produce antioxidant effects, interactions with enzyme **endothelial NO synthase** (eNOS) and effects on cofactor bioavailability of NO. Folate acts indirectly to lower homocysteine levels and insure optimal functioning of the methylation cycle. Folate metabolism provides an interesting example of gene-environmental interaction. A great part of the population, especially subgroups with higher demand, appears to have suboptimal folate intake, as determined through more sensitive parameters now widely determined. The available data strongly suggest that criteria for "folate deficiency" may have to be redefined.

CT Medical Descriptors:
DNA methylation
DNA synthesis
gene expression regulation
genetic transcription
chromatin structure
DNA repair
genetic stability
folic acid deficiency: DI, diagnosis
folic acid deficiency: DT, drug therapy
atherosclerosis: PC, prevention
neurologic disease: PC, prevention
mental disease: PC, prevention
congenital disorder: PC, prevention
carcinogenesis: PC, prevention
diet supplementation
antioxidant activity
protein interaction
endothelium
bioavailability
amino acid blood level
vitamin metabolism
gene interaction
vitamin intake
drug structure
drug metabolism
drug blood level
megaloblastic anemia: DT, drug therapy
megaloblastic anemia: ET, etiology
drug competition
human
nonhuman
controlled study
article
Drug Descriptors:
*folic acid: AN, drug analysis
*folic acid: CM, drug comparison
*folic acid: CR, drug concentration
*folic acid: IT, drug interaction
*folic acid: DT, drug therapy
*folic acid: EC, endogenous compound
*folic acid: PK, pharmacokinetics
*folic acid: PD, pharmacology
*folic acid: PO, oral drug administration
folic acid derivative: AN, drug analysis
folic acid derivative: CM, drug comparison
folic acid derivative: EC, endogenous compound

folic acid derivative: PK, pharmacokinetics
folic acid derivative: PD, pharmacology
carbon: EC, endogenous compound
methionine: EC, endogenous compound
methyl group: EC, endogenous compound
DNA: EC, endogenous compound
enzyme: EC, endogenous compound
nitric oxide synthase: EC, endogenous compound
nitric oxide: EC, endogenous compound
homocysteine: EC, endogenous compound
tetrahydrofolic acid: AN, drug analysis
tetrahydrofolic acid: CM, drug comparison
tetrahydrofolic acid: EC, endogenous compound
tetrahydrofolic acid: PK, pharmacokinetics
tetrahydrofolic acid: PD, pharmacology
dihydrofolic acid: PD, pharmacology
5 methyltetrahydrofolate homocysteine methyltransferase: EC, endogenous compound
methylenetetrahydrofolic acid: AN, drug analysis
methylenetetrahydrofolic acid: CM, drug comparison
methylenetetrahydrofolic acid: PD, pharmacology
thymidylate synthase: EC, endogenous compound
dihydrofolate reductase: EC, endogenous compound
reduced nicotinamide adenine dinucleotide phosphate: EC, endogenous compound
methotrexate: PD, pharmacology
glycine hydroxymethyltransferase: EC, endogenous compound
methionine synthase: EC, endogenous compound
adenosylhomocysteinase: EC, endogenous compound
5,10 methylenetetrahydrofolate reductase (FADH2): EC, endogenous compound
cystathionine beta synthase: EC, endogenous compound
cobalamin: EC, endogenous compound
antibiotic agent
cytostatic agent
sulfonamide: PD, pharmacology
salazosulfapyridine: IT, drug interaction
ascorbic acid: CM, drug comparison
ascorbic acid: PD, pharmacology
RN (folic acid) 59-30-3, 6484-89-5; (carbon) 7440-44-0; (methionine) 59-51-8, 63-68-3, 7005-18-7; (DNA) 9007-49-2; (nitric oxide synthase) 125978-95-2; (nitric oxide) 10102-43-9; (homocysteine) 454-28-4, 6027-13-0; (tetrahydrofolic acid) 135-16-0; (dihydrofolic acid) 25512-82-7; (5 methyltetrahydrofolate homocysteine methyltransferase) 9033-23-2; (methylenetetrahydrofolic acid) 3432-99-3; (thymidylate synthase) 9031-61-2; (dihydrofolate reductase) 9002-03-3; (reduced nicotinamide adenine dinucleotide phosphate) 53-57-6; (methotrexate) 15475-56-6, 59-05-2, 7413-34-5; (glycine hydroxymethyltransferase) 9029-83-8; (methionine synthase) 37290-90-7; (adenosylhomocysteinase) 9025-54-1; (5,10 methylenetetrahydrofolate reductase (FADH2)) 9028-69-7; (cystathionine beta synthase) 9023-99-8; (cobalamin) 13408-78-1; (salazosulfapyridine) 599-79-1; (ascorbic acid) 134-03-2, 15421-15-5, 50-81-7

L54 ANSWER 3 OF 29 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:196584 HCAPLUS
DOCUMENT NUMBER: 137:41169
TITLE: **Nitric oxide** therapies in vascular

diseases
AUTHOR(S): Kurowska, E. M.
CORPORATE SOURCE: KGK Synergize Inc., London, ON, N6A 5R8, Can.
SOURCE: Current Pharmaceutical Design (2002), 8(3), 155-166
CODEN: CPDEFP; ISSN: 1381-6128
PUBLISHER: Bentham Science Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Endothelial dysfunction defined as the impaired ability of vascular endothelium to stimulate vasodilation plays a key role in the development of atherosclerosis and in various pathol. conditions which predispose to atherosclerosis, such as hypercholesterolemia, hypertension, type 2 diabetes, hyperhomocyst (e) inemia and chronic renal failure. The major cause of the endothelial dysfunction is decreased bioavailability of **nitric oxide** (NO), a potent biol. vasodilator produced in vascular endothelium from L-arginine by the **endothelial NO synthase** (eNOS). In vascular diseases, the bioavailability of NO can be impaired by various mechanisms, including decreased NO prodn. by eNOS, and/or enhanced **NO** breakdown due to **increased** oxidative stress. The deactivation of eNOS is often assocd. with elevated plasma levels of its endogenous inhibitor, NG NG-dimethyl-L-arginine (ADMA). In hypercholesterolemia, a systemic deficit of **NO** may also **increase** the levels of low d. lipoproteins (LDL) by modulating its synthesis and metab. by the liver, as suggested by recent in vivo and in vitro studies using org. NO donors. Therapeutic strategies aiming to reduce the risk of vascular diseases by **increasing** bioavailability of **NO** continue to be developed. Cholesterol-lowering drugs, statins, have been shown to improve endothelial function in patients with hypercholesterolemia and atherosclerosis. Promising results were also obtained in some, but not all, vascular diseases after treatment with antioxidant vitamins (C and E) and after administration of eNOS substrate, L-arginine, or its cofactor, tetrahydrobiopterin (BH4). Novel strategies, which may produce beneficial changes in the vascular endothelium, include the use of natural exts. from plant foods rich in phytochems.

CC 1-0 (Pharmacology)
ST review **nitric oxide** vascular disease antioxidant vitamin human
IT Antiarteriosclerotics
(antiatherosclerotics; **nitric oxide** therapies in vascular diseases)
IT Blood vessel, disease
(dysfunction; **nitric oxide** therapies in vascular diseases)
IT Kidney, disease
(failure, chronic; **nitric oxide** therapies in vascular diseases)
IT Lipoproteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(low-d.; **nitric oxide** therapies in vascular diseases)
IT Anticholesteremic agents
Antihypertensives
Drug bioavailability
Human
Vasodilators
(**nitric oxide** therapies in vascular diseases)

IT Vitamins
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**nitric oxide** therapies in vascular diseases)
IT Diabetes mellitus
(non-insulin-dependent; **nitric oxide** therapies in vascular diseases)
IT Antioxidants
(pharmaceutical; **nitric oxide** therapies in vascular diseases)
IT **74-79-3**, L-Arginine, biological studies 125978-95-2, **Nitric oxide** synthase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**nitric oxide** therapies in vascular diseases)
IT **10102-43-9**, **Nitric oxide**, biological studies
17528-72-2, Tetrahydrobiopterin
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**nitric oxide** therapies in vascular diseases)
REFERENCE COUNT: 124 THERE ARE 124 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L54 ANSWER 4 OF 29 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001358784 EMBASE
TITLE: Endothelial dysfunction is induced by proinflammatory oxidant hypochlorous acid.
AUTHOR: Zhang C.; Pate R.; Eiserich J.P.; Zhou F.; Kelpke S.; Ma W.; Parks D.A.; Darley-Usmar V.; White C.R.
CORPORATE SOURCE: C.R. White, Univ. of Alabama at Birmingham, Zeigler Research Bldg, Birmingham, AL 35294, United States. crwhite@uab.edu
SOURCE: American Journal of Physiology - Heart and Circulatory Physiology, (2001) 281/4 50-4 (H1469-H1475).
Refs: 38
ISSN: 0363-6135 CODEN: AJPPDI
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The myeloperoxidase (MPO)-derived oxidant hypochlorous acid (HOCl) plays a role in tissue injury under inflammatory conditions. The present study tests the hypothesis that HOCl decreases nitric oxide (NO) bioavailability in the vasculature of Sprague-Dawley rats. Aortic ring segments were pretreated with HOCl (1-50 .mu.M) followed by extensive washing. Endothelium-dependent relaxation was then assessed by cumulative addition of acetylcholine (ACh) or the calcium ionophore A23187. HOCl treatment significantly impaired both ACh- and A23187-mediated relaxation. In contrast, endothelium-independent relaxation induced by sodium nitroprusside was unaffected. The inhibitory effect of HOCl on ACh-induced relaxation was reversed by exposure of ring segments to L-**arginine** but not D-**arginine**. In cellular studies, HOCl did not alter **endothelial NO synthase** (NOS III) protein or activity, but inhibited formation of the NO metabolites nitrate (NO(3)(-)) and nitrite (NO(2)(-)). The reduction in total NO metabolite production in bovine aortic endothelial cells was also reversed by addition of L-

arginine. These data suggest that HOCl induces endothelial dysfunction via modification of L-**arginine**.

CT Medical Descriptors:
*vascular endothelium
tissue injury
inflammation
bioavailability
vascularization
vascular ring
vasodilatation
cattle
nonhuman
male
rat
controlled study
animal tissue
animal cell
article
priority journal
Drug Descriptors:
*oxidizing agent
*hypochlorous acid
myeloperoxidase
nitric oxide
acetylcholine
calcimycin
nitroprusside sodium
arginine
dextro arginine
nitrate
nitrite

RN (hypochlorous acid) 7790-92-3; (nitric oxide) 10102-43-9; (acetylcholine) 51-84-3, 60-31-1, 66-23-9; (calcimycin) 52665-69-7; (nitroprusside sodium) 14402-89-2, 15078-28-1; (**arginine**) 1119-34-2, 15595-35-4, 7004-12-8, 74-79-3; (nitrate) 14797-55-8; (nitrite) 14797-65-0

L54 ANSWER 5 OF 29 MEDLINE

ACCESSION NUMBER: 2001476149 MEDLINE
DOCUMENT NUMBER: 21410722 PubMed ID: 11518845
TITLE: Effect of calcium antagonist or beta blockade treatment on **nitric oxide**-dependent vasodilation and oxidative stress in essential hypertensive patients.
AUTHOR: Taddei S; Virdis A; Ghiadoni L; Magagna A; Pasini A F; Garbin U; Cominacini L; Salvetti A
CORPORATE SOURCE: Department of Internal Medicine, University of Pisa, Italy.. s.taddei@int.med.unipi.it
SOURCE: JOURNAL OF HYPERTENSION, (2001 Aug) 19 (8) 1379-86. Journal code: 8306882. ISSN: 0263-6352.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20010827
Last Updated on STN: 20020128

Entered Medline: 20020125

AB OBJECTIVES: Essential hypertension is associated with impaired endothelium-dependent vasodilation caused by oxygen free radical-induced **nitric oxide** (NO) breakdown. Since calcium antagonists can improve endothelial function in hypertensive patients, we tested whether this beneficial effect could be related to restoration of NO availability by antioxidant activity. METHODS: In 10 healthy subjects and 20 essential hypertensive patients, we studied forearm blood flow (strain-gauge plethysmography) modifications induced by intrabrachial acetylcholine (from 0.15-15 microg/100 ml per min), bradykinin (0.005-0.05 microg/100 ml per min), two endothelium-dependent vasodilators, and sodium nitroprusside (1-4 microg/100 ml forearm tissue per min), an endothelium independent vasodilator, in the absence and presence of NG-monomethyl-L-**arginine** (L-NMMA) (100 microg/100 ml forearm tissue per min), an NO synthase inhibitor. RESULTS: In controls, vasodilation to acetylcholine and bradykinin was inhibited by L-NMMA. In hypertensive patients, vasodilation to acetylcholine and bradykinin, but not to sodium nitroprusside, was blunted and resistant to L-NMMA. Hypertensive patients were randomized to a 12-week treatment with lacidipine (4-6 mg/daily) or atenolol (50-100 mg/daily) (n = 10 each group). Lacidipine but not atenolol increased the vasodilation to acetylcholine and bradykinin and restored the inhibiting effect of L-NMMA on endothelium-dependent vasodilation, without affecting the response to sodium nitroprusside. Moreover, lacidipine reduced circulating markers of oxidative stress including plasma and low-density lipoprotein (LDL) hydroperoxides, the susceptibility of LDL to Cu2+-induced oxidation and the reactive oxygen species generated from human umbilical vein endothelial cells after incubation with LDL derived from plasma of the patients. CONCLUSIONS: Lacidipine **increases** endothelium-dependent vasodilation by restoring **NO** availability, and this effect possibly is related to antioxidant activity.

CT Check Tags: Female; Human; Male
*Adrenergic beta-Antagonists: TU, therapeutic use
Adult
*Antioxidants: TU, therapeutic use
*Atenolol: TU, therapeutic use
Biological Availability
Biological Markers
*Calcium Channel Blockers: TU, therapeutic use
*Dihydropyridines: TU, therapeutic use
Double-Blind Method
*Hypertension: DT, drug therapy
*Hypertension: PP, physiopathology
Middle Age
Nitric Oxide: BL, blood
***Nitric Oxide: PH, physiology**
*Oxidative Stress: DE, drug effects
*Vasodilation: DE, drug effects
*Vasodilation: PH, physiology

RN **10102-43-9 (Nitric Oxide)**; 103890-78-4 (lacidipine); 29122-68-7 (Atenolol)

CN 0 (Adrenergic beta-Antagonists); 0 (Antioxidants); 0 (Biological Markers); 0 (Calcium Channel Blockers); 0 (Dihydropyridines)

L54 ANSWER 6 OF 29 MEDLINE
ACCESSION NUMBER: 2001266131 MEDLINE
DOCUMENT NUMBER: 21201771 PubMed ID: 11304521

TITLE: C-type natriuretic peptide-induced vasodilation is dependent on hyperpolarization in human forearm resistance vessels.

AUTHOR: Honing M L; Smits P; Morrison P J; Burnett J C Jr; Rabelink T J

CORPORATE SOURCE: Department of Vascular Medicine, University Hospital Utrecht, The Netherlands.

SOURCE: HYPERTENSION, (2001 Apr) 37 (4) 1179-83.
Journal code: 7906255. ISSN: 1524-4563.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200105

ENTRY DATE: Entered STN: 20010529
Last Updated on STN: 20010529
Entered Medline: 20010524

AB Animal studies have demonstrated that CNP causes endothelium-independent vasodilation, which is limited by neutral endopeptidase (NEP) activity. However, the vasodilating mechanism of CNP in humans is still unknown. Therefore, we investigated the vasodilator actions of CNP in human forearm resistance vessels before and after inhibition of **nitric oxide** (NO) and then prostacyclin production and after inhibition of Ca(2+)-dependent potassium channel activation and NEP activity. Three separate studies were performed. In each study, forearm blood flow was recorded by venous occlusion plethysmography in 8 healthy nonsmoking subjects. Brachial artery infusion of CNP (70, 140, 280, and 560 ng per 100 mL forearm volume per minute) caused significant forearm vasodilation in all studies (forearm blood flow from 3.94 to 8.50 mL per 100 mL forearm volume per minute). Inhibition of the endogenous generation of NO by L-N(G)-monomethyl **arginine** (by use of the NO-clamp technique) did not block the maximal vasodilating effects of CNP (forearm blood flow from 3.69 to 6.93). In addition, when the cyclooxygenase system was inhibited by 600 mg of acetylsalicylic acid (aspirin) administered orally 30 minutes before start of measurements, the rise in forearm blood flow remained intact (forearm blood flow from 3.31 to 8.27 mL per 100 mL forearm volume per minute). However, inhibition of Ca(2+)-dependent potassium channels with tetraethylammonium chloride (0.1 mg per 100 mL forearm volume per minute) significantly attenuated vasodilation caused by CNP (forearm blood flow from 2.28 to 3.06 mL per 100 mL forearm volume per minute), which suggests that CNP opens vascular potassium channels. Vasodilation to all doses of CNP was significantly increased when activity of NEP was blocked with thiorphan (30 nmol/min), which suggests that NEP activity limits vasodilation of CNP. CNP is a dilator of human resistance vessels that mediates its effects through hyperpolarization of the vessel wall independent of the **NO** and prostaglandin system. Inhibition of local NEP activity **increases** CNP **bioavailability**. This may be of relevance to cardiovascular disease, given that vascular tone is well balanced between NO and an endothelium-derived hyperpolarizing factor, which suggests that in pathological situations, impaired NO activity can be compensated for by enhanced endothelium-derived hyperpolarizing factor release to maintain vascular homeostasis.

CT Check Tags: Human
Adolescence
Adult
Analysis of Variance

Biological Availability
Cyclooxygenase Inhibitors: PD, pharmacology
Epoprostenol: AI, antagonists & inhibitors
Epoprostenol: PH, physiology
Forearm: BS, blood supply
*Natriuretic Peptide, C-Type: PH, physiology
Neprilysin: AI, antagonists & inhibitors
Neprilysin: ME, metabolism
Nitric Oxide: PH, physiology
Nitric-Oxide Synthase: AI, antagonists & inhibitors
Nitric-Oxide Synthase: PH, physiology
Potassium Channel Blockers
Potassium Channels: ME, metabolism
Prostaglandin-Endoperoxide Synthase: PH, physiology
*Vascular Resistance: PH, physiology
Vasodilation: DE, drug effects
*Vasodilation: PH, physiology
RN **10102-43-9 (Nitric Oxide)**; 127869-51-6 (Natriuretic Peptide, C-Type); 35121-78-9 (Epoprostenol)
CN 0 (Cyclooxygenase Inhibitors); 0 (Potassium Channel Blockers); 0 (Potassium Channels); EC 1.14.13.39 (**Nitric-Oxide** Synthase); EC 1.14.99.1 (Prostaglandin-Endoperoxide Synthase); EC 3.4.24.11 (Neprilysin)

L54 ANSWER 7 OF 29 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001211649 EMBASE
TITLE: Nitric oxide therapy for cardiovascular disease.
AUTHOR: Laight D.W.
CORPORATE SOURCE: D.W. Laight, School of Pharmacy/Biomedical Sci., University of Portsmouth, White Swan Road, Portsmouth PO1 2DT, United Kingdom. david.laight@port.ac.uk
SOURCE: Expert Opinion on Therapeutic Patents, (2001) 11/6 (999-1005).
Refs: 62
ISSN: 1354-3776 CODEN: EOTPEG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
028 Urology and Nephrology
037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Endothelium-derived NO is acknowledged as a key mediator of cardiovascular homeostasis. Indeed, an impairment in endothelial function resulting in limited NO bioavailability may contribute to a raft of vascular pathologies while a failure of peripheral 'nitrergic' neurovasodilator tone is implicated in erectile dysfunction. In addition to the established NO therapy exemplified by the use of nitrovasodilators, the endogenous NO pathway can now be therapeutically modulated to optimise endothelial or peripheral neuronal vasodilator function by inhibiting PDEV. A similar modulation of the NO pathway may also be clinically viable through the supplementation of precursors and cofactors of NO synthesis, the upregulation of **endothelial NO synthase** (eNOS) and the transfection of NOS genes to the vasculature.

CT Medical Descriptors:
*cardiovascular disease: DT, drug therapy
endothelium
homeostasis
drug bioavailability
vascular disease
peripheral nervous system
vasodilatation
blood vessel tone
erectile dysfunction: DT, drug therapy
erectile dysfunction: PC, prevention
modulation
supplementation
precursor
genetic transfection
vascularization
patent
sustained release formulation
drug mechanism
cerebrovascular disease: DT, drug therapy
coronary artery disease: DT, drug therapy
restenosis: DT, drug therapy
restenosis: PC, prevention
peripheral vascular disease: DT, drug therapy
angina pectoris: DT, drug therapy
thrombosis: DT, drug therapy
impotence: DT, drug therapy
female sexual dysfunction: DT, drug therapy
female sexual dysfunction: PC, prevention
congestive heart failure: DT, drug therapy
stroke: DT, drug therapy
diabetic neuropathy: DT, drug therapy
drug potentiation
gene therapy
hypotension: SI, side effect
review
Drug Descriptors:
***nitric oxide: AE, adverse drug reaction**
***nitric oxide: DT, drug therapy**
***nitric oxide: EC, endogenous compound**
***nitric oxide: PR, pharmaceutics**
***nitric oxide: PK, pharmacokinetics**
***nitric oxide: PD, pharmacology**
***nitric oxide: IV, intravenous drug administration**
***nitric oxide: PO, oral drug administration**
***nitric oxide: TD, transdermal drug administration**
vasodilator agent: DT, drug therapy
vasodilator agent: PK, pharmacokinetics
vasodilator agent: PD, pharmacology
vasodilator agent: IV, intravenous drug administration
vasodilator agent: PO, oral drug administration
vasodilator agent: TD, transdermal drug administration
nitric oxide synthase: EC, endogenous compound
arginine: CB, drug combination
arginine: IT, drug interaction
arginine: DT, drug therapy
arginine: PR, pharmaceutics

arginine: PO, oral drug administration
arginine: TP, topical drug administration
alpha 1 adrenergic receptor blocking agent: CB, drug combination
alpha 1 adrenergic receptor blocking agent: DT, drug therapy
hydroxymethylglutaryl coenzyme A reductase inhibitor: CB, drug combination
hydroxymethylglutaryl coenzyme A reductase inhibitor: DT, drug therapy
organic nitrate: DT, drug therapy
organic nitrate: PD, pharmacology
isosorbide mononitrate
nitroprusside sodium
nicorandil
linsidomine: PD, pharmacology
molsidomine: DT, drug therapy
molsidomine: PO, oral drug administration
s nitrosoglutathione: DT, drug therapy
s nitrosoglutathione: EC, endogenous compound
s nitrosoglutathione: PD, pharmacology
nitroso derivative: DT, drug therapy
nitroso derivative: EC, endogenous compound
nitroso derivative: PD, pharmacology
s nitrosoglyco amino acid: DT, drug therapy
s nitrosoglyco amino acid: EC, endogenous compound
s nitrosoglyco amino acid: PD, pharmacology
n acetyl s nitrosopenicillamine
furazolidone: DT, drug therapy
5(6) isopropoxycarbonylbenzofuroxan: DT, drug therapy
nitroxide derivative: DT, drug therapy
nitroxide derivative: PD, pharmacology
nitroxide derivative: IV, intravenous drug administration
nitroxide derivative: PO, oral drug administration
nitroxide derivative: TD, transdermal drug administration
4 nitrooxy 2,2, 6 6 tetramethylpiperinyloxy 4 mononitrate: DT, drug therapy
4 nitrooxy 2,2, 6 6 tetramethylpiperinyloxy 4 mononitrate: PD, pharmacology
4 nitrooxy 2,2, 6 6 tetramethylpiperinyloxy 4 mononitrate: IV, intravenous drug administration
4 nitrooxy 2,2, 6 6 tetramethylpiperinyloxy 4 mononitrate: PO, oral drug administration
4 nitrooxy 2,2, 6 6 tetramethylpiperinyloxy 4 mononitrate: TD, transdermal drug administration
sildenafil: CB, drug combination
sildenafil: IT, drug interaction
sildenafil: DT, drug therapy
sildenafil: PR, pharmaceutics
sildenafil: PD, pharmacology
alpha 1 adrenergic receptor stimulating agent: CB, drug combination
alpha 1 adrenergic receptor stimulating agent: DT, drug therapy
midodrine: CB, drug combination
midodrine: DT, drug therapy
pyrimidinone derivative: DT, drug therapy
pyrimidinone derivative: PR, pharmaceutics
pyrimidinone derivative: PD, pharmacology
pyrazolopyrimidinone: DT, drug therapy
pyrazolopyrimidinone: PR, pharmaceutics
pyrazolopyrimidinone: PD, pharmacology
pentaerythrityl tetranitrate: IT, drug interaction

guanylate cyclase activator: DT, drug therapy
guanylate cyclase activator: PR, pharmaceutics
guanylate cyclase activator: PD, pharmacology
pyrimidine derivative: DT, drug therapy
pyrimidine derivative: PR, pharmaceutics
pyrimidine derivative: PD, pharmacology
4 amino 2 aryl pyrimidine: DT, drug therapy
4 amino 2 aryl pyrimidine: PR, pharmaceutics
4 amino 2 aryl pyrimidine: PD, pharmacology
unindexed drug
unclassified drug

RN (nitric oxide) 10102-43-9; (nitric oxide synthase) 125978-95-2; (**arginine**) 1119-34-2, 15595-35-4, 7004-12-8, 74-79-3; (isosorbide mononitrate) 1320-91-8; (nitroprusside sodium) 14402-89-2, 15078-28-1; (nicorandil) 65141-46-0; (linsidomine) 16142-27-1, 33876-97-0; (molsidomine) 25717-80-0; (s nitrosoglutathione) 57564-91-7; (n acetyl s nitrosopenicillamine) 79032-48-7; (furazolidone) 67-45-8; (sildenafil) 139755-83-2; (midodrine) 3092-17-9, 42794-76-3; (pentaerythrityl tetranitrate) 78-11-5, 8059-08-3

CN (1) Viagra

CO (1) Pfizer

L54 ANSWER 8 OF 29 MEDLINE

ACCESSION NUMBER: 2001537685 MEDLINE

DOCUMENT NUMBER: 21449095 PubMed ID: 11564257

TITLE: Prevention and reversal of experimental posthemorrhagic vasospasm by the periadventitial administration of **nitric oxide** from a controlled-release polymer.

AUTHOR: Tierney T S; Clatterbuck R E; Lawson C; Thai Q A; Rhines L D; Tamargo R J

CORPORATE SOURCE: Department of Neurological Surgery, The Johns Hopkins University School of Medicine, 600 N. Wolfe Street, Baltimore, MD 21287-7713, USA.

SOURCE: NEUROSURGERY, (2001 Oct) 49 (4) 945-51; discussion 951-3. Journal code: 7802914. ISSN: 0148-396X.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200112

ENTRY DATE: Entered STN: 20011008
Last Updated on STN: 20020122
Entered Medline: 20011204

AB OBJECTIVE: Despite improvements in the care of patients with aneurysmal subarachnoid hemorrhage, delayed **cerebral** vasospasm remains a major cause of morbidity and death. There is now evidence that a decrease in the local availability of **nitric oxide** (NO) plays a role in delayed **cerebral** vasospasm. We evaluated a controlled-release polymer containing the NO donor (Z)-1-[2-(2-aminoethyl)-N-(2-ammonioethyl)amino]diazen-1-ium-1,2-diolate (DETA/NO) for the treatment of chronic posthemorrhagic vasospasm in the rat femoral artery model. METHODS: The release kinetics of ethylene/vinyl acetate copolymers loaded with 20% (w/w) DETA/NO were determined in vitro. Chronic vasospasm was induced in the left femoral artery of adult male Fischer 344 rats (n = 35) by exposure to autologous blood. At 1, 3, or 7 days after blood exposure, either a 5-mg polymer loaded with 20% (w/w) DETA/NO or an empty

5-mg polymer was placed in the periadventitial space next to the left femoral artery. At the same time, an empty 5-mg polymer was placed next to the right femoral artery. On the 8th day after blood exposure (at the peak of vasospasm in this model), rats were transcardially perfused with 4% paraformaldehyde, and the left and right femoral arteries were removed for histological processing and morphometric analyses. Vasospasm was expressed as the percent lumen patency of the treated left artery, compared with the control right artery. RESULTS: The in vitro release kinetics demonstrated that the 20% DETA/NO-loaded polymers released up to 15% of their total drug load during a 9-day period. DETA/NO treatments initiated at 1, 3, or 7 days after blood deposition all significantly inhibited vasospasm, compared with control values (94.6 +/- 7.2% versus 67.6 +/- 5.8%, 104.6 +/- 5.5% versus 64.9 +/- 1.7%, and 102.4 +/- 5.1% versus 73.6 +/- 1.4%, respectively; mean +/- standard error of the mean percent lumen patency; $P < 0.001$). No adverse effects of treatment were observed. CONCLUSION: The diazeniumdiolate NO donor DETA/NO can be effectively released from ethylene/vinyl acetate polymers. Administration of DETA/NO into the periadventitial space can prevent the development of chronic posthemorrhagic vasospasm in the rat femoral artery and can reverse established vasospasm. No adverse effects of DETA/NO were observed in this model.

CT Check Tags: Animal; Male
Biological Availability
Delayed-Action Preparations
*Drug Implants
***Nitric Oxide: AD, administration & dosage**
Nitric Oxide: PK, pharmacokinetics
Rats
Rats, Inbred F344
Subarachnoid Hemorrhage: BL, blood
Subarachnoid Hemorrhage: DT, drug therapy
*Triazenes
Vasodilation: DE, drug effects
Vasospasm, Intracranial: BL, blood
*Vasospasm, Intracranial: DT, drug therapy
RN **10102-43-9 (Nitric Oxide)**
CN 0 (1-hydroxy-2-oxo-3,3-bis(2-aminoethyl)-1-triazene); 0 (Delayed-Action Preparations); 0 (Drug Implants); 0 (Triazenes)

L54 ANSWER 9 OF 29 MEDLINE
ACCESSION NUMBER: 2001214774 MEDLINE
DOCUMENT NUMBER: 21112923 PubMed ID: 11171786
TITLE: Comparative effect of ace inhibition and angiotensin II type 1 receptor antagonism on bioavailability of **nitric oxide** in patients with coronary artery disease: role of superoxide dismutase.
AUTHOR: Hornig B; Landmesser U; Kohler C; Ahlersmann D; Spiekermann S; Christoph A; Tatge H; Drexler H
CORPORATE SOURCE: Abteilung Kardiologie und Angiologie, Medizinische Hochschule Hannover, Hannover, Germany.. hornig.burkhard@mh-hannover.de
SOURCE: CIRCULATION, (2001 Feb 13) 103 (6) 799-805. Journal code: 0147763. ISSN: 1524-4539.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL) Journal; Article; (JOURNAL ARTICLE) (RANDOMIZED CONTROLLED TRIAL)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010425
Last Updated on STN: 20010521
Entered Medline: 20010419

AB BACKGROUND: Flow-dependent, endothelium-mediated vasodilation (FDD) and activity of extracellular superoxide dismutase (EC-SOD), the major antioxidative enzyme of the arterial wall, are severely impaired in patients with coronary artery disease (CAD). We hypothesized that both ACE inhibitor (ACEI) and angiotensin II type 1 receptor antagonist (AT(1)-A) **increase bioavailability** of **nitric oxide** (**NO**) by reducing oxidative stress in the vessel wall, possibly by increasing EC-SOD activity. METHODS AND RESULTS: Thirty-five patients with CAD were randomized to 4 weeks of ACEI (ramipril 10 mg/d) or AT(1)-A (losartan 100 mg/d). FDD of the radial artery was determined by high-resolution ultrasound before and after intra-arterial N-monomethyl-L-**arginine** (L-NMMA) to inhibit NO synthase and before and after intra-arterial vitamin C to determine the portion of FDD inhibited by oxygen free radicals. EC-SOD activity was determined after release from endothelium by heparin bolus injection. FDD was improved after ramipril and losartan (each group P<0.01), and in particular, the portion of FDD mediated by **NO**, ie, inhibited by L-NMMA, was **increased** by >75% (each group P<0.01). Vitamin C improved FDD initially, an effect that was lost after ramipril or losartan. After therapy, EC-SOD activity was increased by >200% in both groups (ACEI, 14.4+/-1.1 versus 3.8+/-0.9 and AT(1)-A, 13.5+/-1.0 versus 3.9+/-0.9 U. mL(-1). min(-1); each P<0.01). CONCLUSIONS-Four weeks of therapy with ramipril or losartan improves endothelial function to similar extents in patients with CAD by **increasing** the **bioavailability** of **NO**. Our results suggest that beneficial long-term effects of interference with the renin-angiotensin system may be related to reduction of oxidative stress within the arterial wall, mediated in part by increased EC-SOD activity.

CT Check Tags: Comparative Study; Human
*Angiotensin-Converting Enzyme Inhibitors: TU, therapeutic use
Antioxidants: TU, therapeutic use
Ascorbic Acid: TU, therapeutic use
Biological Availability
*Coronary Disease: DT, drug therapy
Coronary Disease: ME, metabolism
Endothelium, Vascular: EN, enzymology
Enzyme Activation
Losartan: TU, therapeutic use
Middle Age
***Nitric Oxide: ME, metabolism**
Nitric-Oxide Synthase: AI, antagonists & inhibitors
Oxidative Stress
Radial Artery: DE, drug effects
Radial Artery: PA, pathology
Radial Artery: PH, physiology
Ramipril: TU, therapeutic use
*Receptors, Angiotensin: AI, antagonists & inhibitors
Regional Blood Flow: DE, drug effects
Superoxide Dismutase: ME, metabolism
Time Factors
Vasodilation

omega-N-Methylarginine: TU, therapeutic use
RN **10102-43-9 (Nitric Oxide)**; 114798-26-4 (Losartan); 17035-90-4 (omega-N-Methylarginine); 50-81-7 (Ascorbic Acid); 87333-19-5 (Ramipril)
CN 0 (Angiotensin-Converting Enzyme Inhibitors); 0 (Antioxidants); 0 (Receptors, Angiotensin); 0 (angiotensin II type 1 receptor); 0 (angiotensin II type 2 receptor); EC 1.14.13.39 (**Nitric-Oxide** Synthase); EC 1.15.1.1 (Superoxide Dismutase)

L54 ANSWER 10 OF 29 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:180563 HCAPLUS
DOCUMENT NUMBER: 134:361170
TITLE: Nifedipine increases endothelial **nitric oxide** bioavailability by antioxidative mechanisms
AUTHOR(S): Berkels, Reinhard; Egink, Guido; Marsen, Tobias A.; Bartels, Henning; Roesen, Renate; Klaus, Wolfgang
CORPORATE SOURCE: Institute of Pharmacology and Clinic IV of Internal Medicine, University of Cologne, Cologne, 50931, Germany
SOURCE: Hypertension (2001), 37(2, Pt. 1), 240-245
CODEN: HPRTDN; ISSN: 0194-911X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Short-term treatment of the endothelium with dihydropyridine calcium antagonists resulted in an **increased** release in **NO** that is not due to a modulation of L-type calcium channels, because macrovascular endothelial cells do not express this channel. We investigated whether long-term (48 h) treatment of porcine endothelial cell cultures with the dihydropyridine calcium antagonist nifedipine resulted in a similar enhanced NO liberation. Regarding to the underlying mechanism, we examd. whether (1) nifedipine changed the mRNA and protein levels of the constitutive **endothelial NO synthase** (NOS) in endothelial cell cultures or (2) nifedipine exerts an NO protective effect via its antioxidative properties, as revealed in a cell culture model and with native endothelium from porcine coronary arteries. Nifedipine induced a significant time- and concn.-dependent increase (132.+-.47%, 1 .mu.mol/L, 40 min' incubation) in the basal NO liberation (oxyHb assay). This **increased NO** release was not due to elevated NOS (type III) mRNA (Northern blot anal.) and protein (Western blot anal.) levels. However, nifedipine (both short- and long-term treatment) significantly reduced the basal and glucose (20 and 30 mmol/L)-stimulated formation of reactive oxygen species (lucigenin assay) of endothelial cell cultures and native cells. We conclude that the calcium antagonist nifedipine enhances the bioavailability of endothelial NO without significantly altering the NOS (type III) mRNA and protein expression, possibly via an antioxidative protection. This **increased NO** availability may cause part of the vasodilation and might contribute to the antithrombotic, antiproliferative, and antiatherosclerotic effects of dihydropyridine calcium antagonists.
CC 1-8 (Pharmacology)
ST nifedipine endothelium **nitric oxide** bioavailability antioxidative mechanism
IT Blood vessel
(endothelium; nifedipine increases endothelial **nitric oxide** bioavailability by antioxidative mechanisms)

IT **Drug bioavailability**
(nifedipine increases endothelial **nitric oxide** bioavailability by antioxidative mechanisms)
IT Reactive oxygen species
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(nifedipine increases endothelial **nitric oxide** bioavailability by antioxidative mechanisms)
IT Antioxidants
(pharmaceutical; nifedipine increases endothelial **nitric oxide** bioavailability by antioxidative mechanisms)
IT 21829-25-4, Nifedipine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nifedipine increases endothelial **nitric oxide** bioavailability by antioxidative mechanisms)
IT 7782-44-7D, Oxygen, reactive species 125978-95-2, **Nitric oxide** synthase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(nifedipine increases endothelial **nitric oxide** bioavailability by antioxidative mechanisms)
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L54 ANSWER 11 OF 29 MEDLINE
ACCESSION NUMBER: 2001492342 MEDLINE
DOCUMENT NUMBER: 21425819 PubMed ID: 11534850
TITLE: Nisoldipine **increases** the **bioavailability** of endothelial **NO**.
AUTHOR: Berkels R; Roesen R; Bartels H; Purol-Schnabel S; Kirmiziguel I; Farmer H; Born G V; Klaus W
CORPORATE SOURCE: Institute of Pharmacology, University of Cologne, Germany.. Reinhard.Berkels@medizin.uni-koeln.de
SOURCE: NAUNYN-SCHMIEDEBERGS ARCHIVES OF PHARMACOLOGY, (2001 Aug) 364 (2) 110-6.
Journal code: 0326264. ISSN: 0028-1298.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20010906
Last Updated on STN: 20020130
Entered Medline: 20020129
AB Different observations suggest that dihydropyridine calcium antagonists alter endothelial NO release. Therefore, in a first step we investigated whether part of the nisoldipine (a dihydropyridine calcium antagonist with a possible selectivity for coronaries)-induced vasorelaxation was due to an NO release from the endothelium in porcine coronary arteries. Secondly, we directly measured whether nisoldipine **increased NO** release from rabbit aorta or the nisoldipine enantiomers (Bay R 1223, Bay R 1224) from rat aorta. Thirdly, we determined whether nisoldipine exerted antioxidative properties in segments of porcine aorta with intact endothelium. Blocking **endothelial NO synthase** with N-nitro-L-**arginine** resulted in a significant shift of the

relaxation curve to higher concentrations. Accordingly, nisoldipine induced a concentration-dependent release of NO (direct electrochemical detection) from native endothelium which already started at a therapeutical level (1 nmol/l nisoldipine/6.5 +/- 1.2 nmol/l NO). To evaluate whether this effect was due to an antioxidative protection of NO, we examined the influence of nisoldipine on a hyperglycemia (30 mmol/l, 20 min)-induced reactive oxygen species release of vascular endothelium from porcine coronary arteries. Nisoldipine concentration-dependently reduced the reactive oxygen species release (>50%; 10 micromol/l). Moreover, a carbachol-induced NO release (rabbit aorta) which was significantly diminished by hyperglycemia was completely restored in the presence of nisoldipine (3 micromol/l). We conclude that nisoldipine **increases** the **NO bioavailability** which may result in an ameliorated endothelial function.

CT Check Tags: Animal; Female

Biological Availability
Coronary Vessels: DE, drug effects
Coronary Vessels: ME, metabolism
Coronary Vessels: SE, secretion
Dose-Response Relationship, Drug
Endothelium, Vascular: DE, drug effects
*Endothelium, Vascular: ME, metabolism
Endothelium, Vascular: SE, secretion
*Nisoldipine: PD, pharmacology
***Nitric Oxide: ME, metabolism**
Nitric Oxide: SE, secretion
Nitrites: ME, metabolism
Organ Culture
Rabbits
Rats
Rats, Wistar
Reactive Oxygen Species: ME, metabolism
Swine
Vasodilation: DE, drug effects
Vasodilation: PH, physiology
*Vasodilator Agents: PD, pharmacology

RN **10102-43-9 (Nitric Oxide)**; 63675-72-9 (Nisoldipine)
CN 0 (Nitrites); 0 (Reactive Oxygen Species); 0 (Vasodilator Agents)

L54 ANSWER 12 OF 29 DRUGU COPYRIGHT 2002 THOMSON DERWENT
ACCESSION NUMBER: 2002-09176 DRUGU P B E
TITLE: Raloxifene improves endothelial dysfunction in hypertension by reduced oxidative stress and enhanced nitric oxide production.
AUTHOR: Wassmann S; Laufs U; Stamenkovic D; Linz W; Ahlbory K; Roesen R; Sauer H; Nickenig G
CORPORATE SOURCE: Univ.Saarland; Aventis; Univ.Cologne
LOCATION: Homburg, Frankfurt; Cologne, Ger.
SOURCE: Circulation (104, No. 17, Suppl., 102, 2001)
CODEN: CIRCAZ ISSN: 0009-7322
AVAIL. OF DOC.: Universitaetskliniken des Saarlandes, Homburg/Saar, Germany.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

AB The selective estrogen receptor modulator (SERM) raloxifene (RALOX) improved hypertension-induced endothelial dysfunction by

increasing the **bioavailability** of **nitric oxide** (**NO**) in SHR. This was mediated by enhanced **endothelial NO synthase** (eNOS) activity and reduced release of reactive oxygen species (ROS) from vascular cells. These vascular effects led to B.P. reduction and decreased vascular damage in male SHR. (conference abstract: Scientific Sessions of the American Heart Association, Anaheim, California, USA, 2001).

L54 ANSWER 13 OF 29 MEDLINE
ACCESSION NUMBER: 2001530020 MEDLINE
DOCUMENT NUMBER: 21460155 PubMed ID: 11576927
TITLE: Effect of chronic renal failure on **nitric oxide** metabolism.
AUTHOR: Vaziri N D
CORPORATE SOURCE: Division of Nephrology and Hypertension, Departments of Medicine, Physiology and Biophysics, University of California, Irvine, CA, USA.. ndvaziri@uci.edu
SOURCE: AMERICAN JOURNAL OF KIDNEY DISEASES, (2001 Oct) 38 (4 Suppl 1) S74-9. Ref: 28
Journal code: 8110075. ISSN: 1523-6838.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011001
Last Updated on STN: 20020122
Entered Medline: 20011204

AB Chronic renal failure (CRF) is associated with hypertension, endothelial dysfunction, and a strong propensity for arteriosclerotic cardiovascular disease. **Nitric oxide** (NO) is an endogenous modulator with diverse biological functions. Chronic inhibition of NO synthases (NOS) has been shown to cause hypertension and vasculopathy. In light of these considerations, numerous studies have explored the effect of CRF on NO metabolism with the assumption that NO deficiency may be involved in the pathogenesis of cardiovascular and other consequences of uremia. The purpose of this review is to provide a brief overview of the effect of CRF on (1) the bioavailability of NO substrate, L-arginine; (2) the expression of NOS isoforms in the relevant organs; (3) the interaction of NO with reactive oxygen species that are known to be increased in CRF, and (4) the accumulation of uremic inhibitors of NOS.

CT Check Tags: Animal; Human
Arginine: PK, pharmacokinetics
Arteries: ME, metabolism
Biological Availability
Brain: ME, metabolism
Down-Regulation
Endothelin-1: ME, metabolism
Hypertension: ME, metabolism
Kidney: ME, metabolism
*Kidney Failure, Chronic: ME, metabolism
***Nitric Oxide: ME, metabolism**
Nitric-Oxide Synthase: AI, antagonists & inhibitors
Nitric-Oxide Synthase: ME, metabolism
Oxidative Stress

Protein Isoforms
Reactive Oxygen Species: ME, metabolism
Up-Regulation
RN **10102-43-9 (Nitric Oxide)**; 74-79-3 (Arginine)
CN 0 (Endothelin-1); 0 (Protein Isoforms); 0 (Reactive Oxygen Species); EC 1.14.13.39 (**Nitric-Oxide** Synthase)

L54 ANSWER 14 OF 29 HCAPLUS COPYRIGHT 2002 ACS DUPLICATE 1
ACCESSION NUMBER: 2000:688084 HCAPLUS
DOCUMENT NUMBER: 133:271636
TITLE: Increasing **cerebral bioavailability** of drugs by stimulating increased production of **nitric oxide**.
INVENTOR(S): Moskowitz, Michael A.; Liao, James K.; Ron, Eyal S.; Omstead, Mary Nallin
PATENT ASSIGNEE(S): Enos Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000056328	A1	20000928	WO 2000-US7089	20000320
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1175210	A1	20020130	EP 2000-919452	20000320
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.:
US 1999-139484P P 19990319
US 1999-138578P P 19990611
US 1999-155485P P 19990923
WO 2000-US7089 W 20000320

AB A method and compns. are provided for increased **cerebral bioavailability** of blood-born compns. by administering the compn. of interest while **increasing** brain **NO** levels. This **increase** in **NO** levels may be accomplished by stimulating **increased** prodn. of **NO** by **endothelial NO synthase** (eNOS), esp. by administering L-arginine, by administering agents that **increase NO** levels independent of **ecNOS**, or by any combination of these methods. As **NO** is **increased**, cerebral blood flow is consequently increased, and drugs in the blood stream are carried along with the increased flow into brain tissue. By increased flow, the site of action will be exposed to more drug mols. By stimulating **increased NO** prodn., administration of drugs that are not easily introduced to the brain may be facilitated and/or the serum concn. necessary to achieve desired physiol. effects may be reduced.

Examples were given showing the effect of L-arginine on cerebral blood flow and compns. contg. L-arginine and simvastatin.

IC ICM A61K031-195
ICS A61K031-519

CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 1

ST brain drug bioavailability **nitric oxide**; arginine brain drug bioavailability

IT Brain
Drug bioavailability
(increasing **cerebral bioavailability** of drugs by stimulating increased prodn. of **nitric oxide**.)

IT Brain, disease
(stroke, ischemic; increasing **cerebral bioavailability** of drugs by stimulating increased prodn. of **nitric oxide**.)

IT **10102-43-9, Nitric oxide**, biological studies
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(increasing **cerebral bioavailability** of drugs by stimulating increased prodn. of **nitric oxide**.)

IT **74-79-3**, L-Arginine, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(increasing **cerebral bioavailability** of drugs by stimulating increased prodn. of **nitric oxide**.)

IT 533-45-9, Clomethiazole 77086-22-7, MK-801 79902-63-9, Simvastatin 139639-23-9, Tissue plasminogen activator 171049-14-2, Lotrafiban
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(increasing **cerebral bioavailability** of drugs by stimulating increased prodn. of **nitric oxide**.)

IT 125978-95-2, **Nitric oxide** synthase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(increasing **cerebral bioavailability** of drugs by stimulating increased prodn. of **nitric oxide**.)

IT **53-57-6**, Nadph **17528-72-2**, Tetrahydrobiopterin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(increasing **cerebral bioavailability** of drugs by stimulating increased prodn. of **nitric oxide**.)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L54 ANSWER 15 OF 29 MEDLINE
ACCESSION NUMBER: 2000192259 MEDLINE
DOCUMENT NUMBER: 20192259 PubMed ID: 10725285
TITLE: Effect of native and oxidized low-density lipoprotein on endothelial **nitric oxide** and superoxide production : key role of L-**arginine** availability.
AUTHOR: Vergnani L; Hatrik S; Ricci F; Passaro A; Manzoli N; Zuliani G; Brovkovych V; Fellin R; Malinski T
CORPORATE SOURCE: Second Department of Internal Medicine, University of Ferrara, Italy.
CONTRACT NUMBER: HL55397 (NHLBI)
SOURCE: CIRCULATION, (2000 Mar 21) 101 (11) 1261-6.

Journal code: 0147763. ISSN: 1524-4539.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000421
Last Updated on STN: 20010521
Entered Medline: 20000412

AB BACKGROUND: Native and oxidized LDLs (n-LDL and ox-LDL) are involved in the atherogenic process and affect endothelium-dependent vascular tone through their interaction with **nitric oxide** (NO).
METHODS AND RESULTS: In this study we evaluated directly, by using a porphyrinic microsensor, the effect of **increasing** lipoprotein concentrations on endothelial **NO** and superoxide (O(2)(-)) production. We investigated where lipoproteins may affect the L-**arginine**-NO pathway by pretreating cells with L-**arginine**, L-N-**arginine** methyl ester (L-NAME), and superoxide dismutase. Bovine aortic endothelial cells were exposed for 1 hour to increasing concentrations of n-LDL (from 0 to 240 mg cholesterol/dL) and ox-LDL (from 0 to 140 mg cholesterol/dL). A stimulated (calcium ionophore) NO concentration decreased to 29% of the control at n-LDL concentration of 80 mg cholesterol/dL and to 15% of the control at 20 mg cholesterol/dL of ox-LDL. L-**Arginine** partially neutralized the inhibitory effect of n-LDL and ox-LDL on the NO generation. Superoxide dismutase pretreatment did not modify NO production, whereas L-NAME blunted NO generation at all LDL concentrations. O(2)(-) production was increased at low n-LDL and very low ox-LDL concentrations; this was reversed by L-**arginine**. CONCLUSIONS: These findings confirm the inhibitory role of n-LDL and ox-LDL on NO generation and suggest that lipoproteins may induce a decreased uptake of L-**arginine**. The local depletion of the L-**arginine** substrate may derange the NO synthase, leading to overproduction of O(2)(-) from oxygen, the other substrate of NO synthase.

CT Check Tags: Animal; Support, U.S. Gov't, P.H.S.
Arginine: PK, pharmacokinetics
Arginine: PD, pharmacology
Biological Availability
Cattle
Cells, Cultured
Endothelium, Vascular: CY, cytology
Endothelium, Vascular: DE, drug effects
*Endothelium, Vascular: ME, metabolism
*Lipoproteins, LDL: PD, pharmacology
Nitric Oxide: AI, antagonists & inhibitors
***Nitric Oxide: BI, biosynthesis**
Superoxides: AI, antagonists & inhibitors
*Superoxides: ME, metabolism

RN **10102-43-9 (Nitric Oxide)**; 11062-77-4 (Superoxides); **74-79-3 (Arginine)**

CN 0 (Lipoproteins, LDL); 0 (oxidized low density lipoprotein)

L54 ANSWER 16 OF 29 DRUGU COPYRIGHT 2002 THOMSON DERWENT
ACCESSION NUMBER: 2000-45838 DRUGU P B
TITLE: Differences in receptor and substrate mediated stimulation of **endothelial NO synthase**: a mechanistic clue for the antiatherogenic properties of l-**arginine**.

AUTHOR: Kelm M; Lauer T; Rassaf Haghigat T; Feelisch M; Weber H; Rosen P; Kuhn Velten N; Reinauer H; Strauer B E
CORPORATE SOURCE: Univ.Dusseldorf; Univ.Louisiana; Univ.Heinrich-Heine
LOCATION: Dusseldorf, Ger.; Shreveport, La., USA
SOURCE: Eur.Heart J. (21, Abstr.Suppl., 271, 2000)
CODEN: EHJODF ISSN: 0195-668X
AVAIL. OF DOC.: Cardiology Department, University of Duesseldorf, Duesseldorf, Germany.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The antiatherogenic properties of l-**arginine** (ARG) infusion were investigated in 26 volunteers and in vitro in porcine aortic endothelial cells (PECs). It is concluded that ARG selectively **increases** the concentration of **NO** at the luminal surface of vascular endothelium. This enhanced **bioavailability** of **NO** is achieved by an **increase** of **NO** production paralleled by a decrease in **endothelial NO synthase** (eNOS) related generation of superoxide and peroxynitrite radicals. These mechanisms may provide a rationale for the anti-atherogenic properties of ARG. (conference abstract: XXII Congress of the European Society of Cardiology, Amsterdam, The Netherlands, 2000).

L54 ANSWER 17 OF 29 MEDLINE
ACCESSION NUMBER: 2000141646 MEDLINE
DOCUMENT NUMBER: 20141646 PubMed ID: 10675697
TITLE: Nasal absorption of (S)-UH-301 and its transport into the **cerebrospinal** fluid of rats.
AUTHOR: Dahlin M; Bjork E
CORPORATE SOURCE: Department of Pharmacy, Division of Pharmaceutics, Biomedical Centre, Uppsala University, Box 580, SE-751 23, Uppsala, Sweden.
SOURCE: INTERNATIONAL JOURNAL OF PHARMACEUTICS, (2000 Feb 15) 195 (1-2) 197-205.
Journal code: 7804127. ISSN: 0378-5173.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000413
Last Updated on STN: 20000413
Entered Medline: 20000403
AB Targeting the **brain** via nasal administration of drugs has been studied frequently over the last few years. In this study, the serotonin-1a receptor antagonist (S)-5-fluoro-8-hydroxy-2-(dipropyl-amino) tetralin ((S)-UH-301) hydrochloride was used as a model substance. The systemic absorption and transport of (S)-UH-301 into male Sprague-Dawley rat **cerebrospinal** fluid (CSF) were investigated after nasal and intravenous administration. Blood and CSF samples were obtained at regular time intervals from the arteria carotis and by cisternal puncture, respectively, after administration to both nostrils (total 12 micromol/kg) or into the vena jugularis (6 micromol/kg). The concentrations of (S)-UH-301 in plasma and CSF were measured by HPLC with electrochemical detection. The maximum plasma concentration of intranasal (S)-UH-301 occurred in about 7 min and the absolute bioavailability seemed to be

complete (F=1.2+/-0.4). Initially, **no increased** concentrations of (S)-UH-301 were seen in CSF after nasal compared to intravenous administration i.e. it appeared that no direct transport of (S)-UH-301 from the nasal cavity, along the olfactory neurons and into the CSF occurred. However, a prolonged duration of the concentration was seen after nasal administration of (S)-UH-301 and after about 20 min the CSF(na):CSF(iv) concentration ratio (corrected for different dosage) exceeded 1.

CT Check Tags: Animal; Comparative Study; Male; Support, Non-U.S. Gov't
8-Hydroxy-2-(di-n-propylamino)tetralin: AD, administration & dosage
*8-Hydroxy-2-(di-n-propylamino)tetralin: AA, analogs & derivatives
8-Hydroxy-2-(di-n-propylamino)tetralin: BL, blood
8-Hydroxy-2-(di-n-propylamino)tetralin: CF, cerebrospinal fluid
8-Hydroxy-2-(di-n-propylamino)tetralin: PK, pharmacokinetics
Absorption
Administration, Inhalation
Area Under Curve
Biological Availability
Chromatography, High Pressure Liquid
Injections, Intravenous
*Nasal Cavity: ME, metabolism
Rats
Rats, Sprague-Dawley
Serotonin Antagonists: AD, administration & dosage
Serotonin Antagonists: BL, blood
Serotonin Antagonists: CF, cerebrospinal fluid
*Serotonin Antagonists: PK, pharmacokinetics
Tissue Distribution

RN 127126-21-0 (UH 301); 78950-78-4 (8-Hydroxy-2-(di-n-propylamino)tetralin)
CN 0 (Serotonin Antagonists)

L54 ANSWER 18 OF 29 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:296464 HCAPLUS
DOCUMENT NUMBER: 135:352849
TITLE: Clinical and biological investigation of **nitric oxide**
AUTHOR(S): Darblade, Benoit; Privat, Christelle; Caillaud, Dominique; Rami, Jacques; Arnal, Jean-Francois
CORPORATE SOURCE: INSERM U397 et Physiologie medicale, CHU Rangueil, Toulouse, 31403, Fr.
SOURCE: Journal de la Societe de Biologie (2000), 194(3-4), 151-157
CODEN: JDSBFG; ISSN: 1295-0661
PUBLISHER: SGS
DOCUMENT TYPE: Journal; General Review
LANGUAGE: French

AB A review with refs. Furchgott et al. demonstrated in 1980 that relaxation of arterial smooth muscle cells in response to acetylcholine is dependent on the integrity of endothelium. They named the factor responsible of this intercellular relationship EDRF (Endothelium Derived Relaxing Factor), which was identified 7 yr latter as **nitric oxide** (NO), a free radical gas. In vessels, NO is generated locally by the **endothelial NO synthase** and its effect is mainly paracrine (relaxation of the underlying smooth muscle cells, and inhibition of platelet aggregation). The in vivo half-life of NO is short, and the assessment of its prodn. is thus difficult. Invasive and non invasive techniques are now available to explore the variations of

arterial diam. or flow. Furchgott's pioneering work anticipated the whole pathophysiol. of endothelial-dependent relaxation. Indeed, numerous diseases, in particular atherosclerosis, are accompanied by abnormalities of endothelial-dependent vasodilation (.mchlt. endothelial dysfunction .mchgt.). Whereas acetylcholine (or serotonin) infused in a normal artery elicits a vasodilation, in contrast, it promotes a vasoconstriction in an atheromatous artery, as a consequence of a decrease in NO bioavailability. This defect in NO favors arterial spasm, interaction between platelets and arterial wall and thrombosis, and thus probably cardiovascular events. NO cannot be measured directly in humans, except in exhaled NO. In vivo, NO is rapidly oxidized in nitrite (NO2-) and in nitrate (NO3-), the summation being NOx. We shall detail the limitations of this measurement as a biochem. index of NO prodn. from .mchlt. endothelial .mchgt. origin.

CC 2-0 (Mammalian Hormones)
Section cross-reference(s): 13

ST review bioavailability **nitric oxide** synthase atherosclerosis endothelium nitrite nitrate

IT Atherosclerosis
Bioavailability
(clin. and biol. investigation of **nitric oxide**)

IT Blood vessel
(endothelium; clin. and biol. investigation of **nitric oxide**)

IT 14797-55-8, Nitrate (NO3-), biological studies 14797-65-0, Nitrite (NO2-), biological studies
RL: ANT (Analyte); BSU (Biological study, unclassified); MFM (Metabolic formation); ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative)
(clin. and biol. investigation of **nitric oxide**)

IT 50-67-9, Serotonin, biological studies 51-84-3, Acetylcholine, biological studies 125978-95-2, **Nitric oxide** synthase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(clin. and biol. investigation of **nitric oxide**)

IT **10102-43-9, Nitric oxide**, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(clin. and biol. investigation of **nitric oxide**)

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L54 ANSWER 19 OF 29 MEDLINE
ACCESSION NUMBER: 2000091298 MEDLINE
DOCUMENT NUMBER: 20091298 PubMed ID: 10625313
TITLE: Effects of long-term nitroglycerin treatment on endothelial **nitric oxide** synthase (NOS III) gene expression, NOS III-mediated superoxide production, and vascular NO bioavailability.
AUTHOR: Munzel T; Li H; Mollnau H; Hink U; Matheis E; Hartmann M; Oelze M; Skatchkov M; Warnholtz A; Duncker L; Meinertz T; Forstermann U
CORPORATE SOURCE: University Hospital Eppendorf, Division of Cardiology, Hamburg, and the Department of Pharmacology, Johannes Gutenberg University, Mainz, Germany.. muenzel@uke.uni-hamburg.de
SOURCE: CIRCULATION RESEARCH, (2000 Jan 7) 86 (1) E7-E12.
Journal code: 0047103. ISSN: 1524-4571.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000124
Last Updated on STN: 20010521
Entered Medline: 20000112

AB Long-term nitroglycerin (NTG) treatment has been shown to be associated with cross-tolerance to endothelium-dependent vasodilators. It may involve increased production of reactive oxygen species (such as superoxide, O(2)(.-)) that rapidly inactivate the **nitric oxide** (NO) released from the endothelial cells. It remains to be elucidated, however, whether long-term treatment with NTG alters the activity and expression of the **endothelial NO synthase** (NOS III) and whether this enzyme can contribute to O(2)(.-) formation. We studied the influence of long-term NTG treatment on the expression of NOS III as assessed by RNase protection assay and Western blot. Tolerance was measured ex vivo in organ chamber experiments with rat aortic rings. O(2)(.-) and NO formation were quantified using lucigenin- and Cypridina luciferin analog-enhanced chemiluminescence as well as electron spin resonance (ESR) spectroscopy. Treatment of Wistar rats with NTG (Alzet osmotic minipumps, NTG concentration 10 microg x kg(-1) x min(-1)) for 3 days caused marked tolerance, cross-tolerance to the endothelium-dependent vasodilator acetylcholine, and a significant increase in O(2)(.-)-induced chemiluminescence. Tolerance was associated with a significant **increase** in **NOS** III mRNA to 236+/-28% and **NOS** III protein to 239+/-17%. In control vessels, the **NOS** inhibitor N(G)-nitro-L-**arginine** (L-NNA) **increased** the O(2)(.-)-mediated chemiluminescence, indicating that basal production of endothelium-derived NO depresses the baseline chemiluminescence signal. In the setting of tolerance, however, L-NNA decreased steady-state O(2)(.-) levels, indicating the involvement of NOS III in O(2)(.-) formation. Likewise, A23187-induced, NOS III-mediated O(2)(.-) production was more pronounced in tolerant than in control vessels. Vascular NO bioavailability as assessed with ESR spectroscopy using iron-thiocarbamate as a trap for NO was significantly reduced in tolerant vessels. Pretreatment of tolerant tissue in vitro with the protein kinase C (PKC) inhibitors reduced basal and stimulated NOS III-mediated O(2)(.-) production and partially reversed vascular tolerance. These findings suggest that NTG treatment **increases** the expression of a dysfunctional **NOS** III gene, leading to **increased** formation of O(2)(.-) and decreased vascular **NO** **bioavailability**. Normalization of NOS III-mediated O(2)(. -) production and improvement of tolerance with PKC inhibition suggests an important role for PKC isoforms in mediating vascular dysfunction caused by long-term NTG treatment.

CT Check Tags: Animal; Support, Non-U.S. Gov't
Acetylcholine: PD, pharmacology
Arginine: PD, pharmacology
Biological Availability
Calcimycin: PD, pharmacology
Carbazoles: PD, pharmacology
Cloning, Molecular
Endothelium, Vascular: DE, drug effects
*Endothelium, Vascular: ME, metabolism
Enzyme Inhibitors: PD, pharmacology

Gene Expression Regulation, Enzymologic: DE, drug effects
Indoles: PD, pharmacology
***Nitric Oxide: ME, metabolism**
Nitric-Oxide Synthase: BI, biosynthesis
***Nitric-Oxide Synthase: GE, genetics**
*Nitroglycerin: PD, pharmacology
Phenanthridines: PD, pharmacology
Protein Kinase C: AI, antagonists & inhibitors
Protein Kinase C: PH, physiology
RNA, Messenger: BI, biosynthesis
Rats
Rats, Wistar
*Superoxides: ME, metabolism
Time
Vasodilation: DE, drug effects

RN **10102-43-9 (Nitric Oxide)**; 11062-77-4 (Superoxides); 136194-77-9 (Go 6976); 34316-15-9 (chelerythrine); 51-84-3 (Acetylcholine); 52665-69-7 (Calcimycin); 55-63-0 (Nitroglycerin); **74-79-3 (Arginine)**

CN 0 (Carbazoles); 0 (Enzyme Inhibitors); 0 (Indoles); 0 (Phenanthridines); 0 (RNA, Messenger); EC 1.14.13.- (endothelial constitutive **nitric oxide** synthase); EC 1.14.13.39 (**Nitric-Oxide** Synthase); EC 2.7.1.- (Protein Kinase C)

L54 ANSWER 20 OF 29 MEDLINE
ACCESSION NUMBER: 2000014317 MEDLINE
DOCUMENT NUMBER: 20014317 PubMed ID: 10548281
TITLE: Coenzyme Q10 does not prevent oral dyskinesias induced by long-term haloperidol treatment of rats.
AUTHOR: Andreassen O A; Weber C; Jorgensen H A
CORPORATE SOURCE: Department of Physiology, University of Bergen, Norway.
SOURCE: PHARMACOLOGY, BIOCHEMISTRY AND BEHAVIOR, (1999 Nov) 64 (3) 637-42.
Journal code: 0367050. ISSN: 0091-3057.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991213

AB Tardive dyskinesia (TD) is a debilitating side effect of long-term treatment with neuroleptics with an unclear pathophysiologic basis. It has been proposed that TD may be a result of neuroleptic-induced oxidative stress. To investigate this hypothesis, we studied if neuroleptic-induced oral dyskinesias in rats, a putative analogue to human TD, could be prevented by the antioxidant coenzyme Q10 (CoQ10). Rats received 16 weeks of treatment with haloperidol decanoate (HAL) IM alone or together with orally administered CoQ10, and the behavior was recorded during and after treatment. HAL significantly increased the level of oral dyskinesias, and the increase persisted for 12 weeks after drug withdrawal. Cotreatment with CoQ10 did not attenuate the development of HAL-induced oral dyskinesia. Despite adequate absorption of orally administered CoQ10, shown by the increased serum levels of CoQ10, **no increase** of either CoQ10 or coenzyme Q9 was detected in the **brain**. These results suggest that cotreatment with CoQ10 does not inhibit the development of HAL-induced oral dyskinesias in rats, and that

further studies seem to be needed in order to clarify the pharmacokinetics of CoQ10 in rats.

CT Check Tags: Animal; Male; Support, Non-U.S. Gov't
Antioxidants: PK, pharmacokinetics
*Antioxidants: PD, pharmacology
*Antipsychotic Agents, Butyrophenone: TO, toxicity
Behavior, Animal: DE, drug effects
Biological Availability
Brain: ME, metabolism
*Dyskinesia, Drug-Induced: PC, prevention & control
*Haloperidol: TO, toxicity
Motor Activity: DE, drug effects
Mouth: PH, physiology
Rats
Rats, Sprague-Dawley
*Ubiquinone: AA, analogs & derivatives
Ubiquinone: PK, pharmacokinetics
Ubiquinone: PD, pharmacology

RN 1339-63-5 (Ubiquinone); 303-98-0 (coenzyme Q10); 52-86-8 (Haloperidol)
CN 0 (Antioxidants); 0 (Antipsychotic Agents, Butyrophenone)

L54 ANSWER 21 OF 29 MEDLINE
ACCESSION NUMBER: 1999429201 MEDLINE
DOCUMENT NUMBER: 99429201 PubMed ID: 10501093
TITLE: Tissue oxygenation modifies **nitric oxide** bioavailability.
AUTHOR: Heyman S N; Goldfarb M; Darmon D; Brezis M
CORPORATE SOURCE: Department of Medicine, Hadassah Hospital-Mt. Scopus and the Hebrew University Medical School, Jerusalem, Israel.
SOURCE: MICROCIRCULATION, (1999 Sep) 6 (3) 199-203. Ref: 37
Journal code: 9434935. ISSN: 1073-9688.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991101
Last Updated on STN: 19991101
Entered Medline: 19991021

AB OBJECTIVE: Because changes in blood oxygenation acutely alter vascular tone, we explored a possible modulation of **nitric oxide** -induced vasodilation (nitrovasodilation) by oxygen. METHODS: We studied the effects of manipulation of tissue oxygenation on renal parenchymal **nitric oxide** (NO) with a selective NO electrode placed in the well-oxygenated renal cortex or in the physiologically hypoxemic outer medulla. RESULTS: In the cortex, as expected, NO signals fell in response to the NO synthase (NOS) inhibitor L-NAME. By contrast, in the outer medulla, NO signals paradoxically rose following NOS inhibition, known to intensify local hypoxia. Other manipulations that intensify outer medullary hypoxia (such as indomethacin or radiologic contrast media) **increased** local **NO** readings, while measures known to ameliorate outer medullary hypoxia (furosemide, L-**arginine**, hypotension) reduced regional NO readings. CONCLUSIONS: Oxygen appears to modulate NO bioavailability, in particular, in tissues with low ambient pO2, perhaps through enhanced binding to oxygenated hemoglobin. It is

proposed that this phenomenon may participate in physiological microvascular regulation, with hypoxemia enhancing NO concentration, while hyperoxemia resulting in accelerated NO removal.

CT Check Tags: Animal
Biological Availability
Kidney: BS, blood supply
Kidney: EN, enzymology
Kidney: ME, metabolism
Microcirculation
***Nitric Oxide: PK, pharmacokinetics**
*Oxygen Consumption: PH, physiology
Rats
Vasodilation

RN **10102-43-9 (Nitric Oxide)**

L54 ANSWER 22 OF 29 MEDLINE
ACCESSION NUMBER: 1998122355 MEDLINE
DOCUMENT NUMBER: 98122355 PubMed ID: 9462523
TITLE: 5-methyltetrahydrofolate, the active form of folic acid, restores endothelial function in familial hypercholesterolemia.
AUTHOR: Verhaar M C; Wever R M; Kastelein J J; van Dam T; Koomans H A; Rabelink T J
CORPORATE SOURCE: Department of Nephrology, University Hospital Utrecht, The Netherlands.
SOURCE: CIRCULATION, (1998 Jan 27) 97 (3) 237-41.
Journal code: 0147763. ISSN: 0009-7322.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980306
Last Updated on STN: 19980306
Entered Medline: 19980223

AB BACKGROUND: Impaired **nitric oxide** (NO) activity is an early event in the pathogenesis of cardiovascular disease, resulting from either reduced **NO** formation or **increased NO** degradation. Administration of **tetrahydrobiopterin** (BH4), an essential cofactor for NO production, could restore NO activity in familial hypercholesterolemia (FH). Because folates have been suggested to stimulate endogenous BH4 regeneration, we hypothesized that administration of 5-methyltetrahydrofolate (5-MTHF, the active circulating form of folate) might improve NO formation in FH. METHODS AND RESULTS: We studied the effects of 5-MTHF on NO bioavailability in vivo in 10 patients with FH and 10 matched control subjects by venous occlusion plethysmography, using serotonin and nitroprusside as endothelium-dependent and -independent vasodilators. In vitro, we investigated the effect of 5-MTHF on NO production by recombinant **endothelial NO synthase** (eNOS) by use of [3H]**arginine** to [3H]citrulline conversion. We also studied the effects of 5-MTHF on superoxide generation by eNOS and xanthine oxidase (XO) by use of lucigenin chemiluminescence. The impaired endothelium-dependent vasodilation in FH (63% versus 90% in control subjects) could be reversed by coinfusion of 5-MTHF (117% vasodilation), whereas 5-MTHF had no significant effect on

endothelium-dependent vasodilation in control subjects. 5-MTHF did not influence basal forearm vasomotion or endothelium-independent vasodilation. 5-MTHF had no direct effect on in vitro NO production by eNOS. However, we did observe a dose-dependent reduction in both eNOS- and XO-induced superoxide generation. CONCLUSIONS: These results show that the active form of folic acid restores in vivo endothelial function in FH. It is suggested from our in vitro experiments that this effect is due to reduced catabolism of NO.

CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't
Adult
Biological Availability
Dose-Response Relationship, Drug
Endothelium: CY, cytology
*Endothelium: DE, drug effects
*Endothelium: PH, physiology
*Folic Acid
Folic Acid: BL, blood
Folic Acid: DE, drug effects
Hemodynamics: DE, drug effects
Homocysteine: BL, blood
Homocysteine: DE, drug effects
*Hypercholesterolemia, Familial: DT, drug therapy
Hypoxanthine: ME, metabolism
Nitric Oxide: ME, metabolism
Nitric Oxide: PK, pharmacokinetics
Nitric-Oxide Synthase: CH, chemistry
Nitric-Oxide Synthase: DE, drug effects
Nitric-Oxide Synthase: ME, metabolism
Recombinant Proteins: CH, chemistry
Recombinant Proteins: DE, drug effects
Recombinant Proteins: ME, metabolism
Superoxides: CH, chemistry
Superoxides: ME, metabolism
Tetrahydrofolates: AD, administration & dosage
*Tetrahydrofolates: PD, pharmacology
Vasodilation: DE, drug effects
Xanthine Oxidase: DE, drug effects
Xanthine Oxidase: ME, metabolism

RN **10102-43-9 (Nitric Oxide)**; 11062-77-4 (Superoxides); 134-35-0 (5-methyltetrahydrofolate); 454-28-4 (Homocysteine); 59-30-3 (Folic Acid); 68-94-0 (Hypoxanthine)

CN 0 (Recombinant Proteins); 0 (Tetrahydrofolates); EC 1.1.3.22 (Xanthine Oxidase); EC 1.14.13.39 (**Nitric-Oxide** Synthase)

L54 ANSWER 23 OF 29 MEDLINE
ACCESSION NUMBER: 1998361285 MEDLINE
DOCUMENT NUMBER: 98361285 PubMed ID: 9697820
TITLE: **Increased bioavailability** of **nitric oxide** after lipid-lowering therapy in hypercholesterolemic patients: a randomized, placebo-controlled, double-blind study.
AUTHOR: John S; Schlaich M; Langenfeld M; Weihprecht H; Schmitz G; Weidinger G; Schmieder R E
CORPORATE SOURCE: Department of Medicine IV, University of Erlangen-Nurnberg, Klinikum Nurnberg-Sud, Germany.
SOURCE: CIRCULATION, (1998 Jul 21) 98 (3) 211-6.
Journal code: 0147763. ISSN: 0009-7322.

PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980910
Last Updated on STN: 19980910
Entered Medline: 19980828

AB BACKGROUND: Impaired endothelium-dependent vasodilation is an early sign of atherosclerosis in hypercholesterolemic patients. We hypothesized that lipid-lowering therapy can improve endothelial function and that this effect is mainly mediated by **increased bioavailability** of **nitric oxide** (**NO**). METHODS AND RESULTS: In a randomized, double-blind, placebo-controlled trial, we studied 29 patients (age, 50+/-12 years) with hypercholesterolemia (LDL cholesterol > or = 160 mg/dL) randomly assigned to receive either fluvastatin (40 mg twice daily; 17 patients) or placebo (12 patients). Forearm blood flow was measured by plethysmography before and after 24 weeks of treatment. Endothelium-dependent vasodilation was assessed by intra-arterial infusion of acetylcholine (ACh; 3, 12, 24, and 48 microg/min) and basal NO synthesis rate by intra-arterial infusion of NG-monomethyl-L-**arginine** (L-NMMA; 1, 2, and 4 micromol/min). Simultaneous intra-arterial infusion of L-NMMA (4 micromol/min) and ACh (12, 24, and 48 microg/min) was used to test whether any increase in endothelium-dependent vasodilation after lipid-lowering therapy could be blocked by this NO synthase inhibitor. Endothelium-dependent vasodilation improved significantly after 24 weeks of lipid-lowering therapy compared with before therapy (ACh 24 microg/min: 240+/-34% before versus 347+/-50% after therapy; P< or =0.01) and placebo (changes between after and before therapy with ACh 24 microg/min: 108+/-39% for fluvastatin versus -26+/-32% for placebo; P< or =0.05). This improvement in endothelium-dependent vasodilation could be blocked by simultaneous administration of L-NMMA (ACh 24 microg/min plus L-NMMA 4 micromol/min: 170+/-69% before versus 219+/-47% after treatment; P=NS). CONCLUSIONS: Lipid-lowering therapy with fluvastatin can improve disturbed endothelial function in hypercholesterolemic patients compared with placebo. This improvement is mediated by **increased bioavailability** of **NO**.

CT Check Tags: Female; Human; Male
Acetylcholine: PD, pharmacology
Adult
*Antilipemic Agents: TU, therapeutic use
Biological Availability
Double-Blind Method
Drug Combinations
Enzyme Inhibitors: PD, pharmacology
Forearm: BS, blood supply
*Hypercholesterolemia: BL, blood
*Hypercholesterolemia: DT, drug therapy
Lipids: BL, blood
Middle Age
***Nitric Oxide: BL, blood**
Nitroprusside: PD, pharmacology
Placebos
Regional Blood Flow: DE, drug effects
Vasodilator Agents: PD, pharmacology

omega-N-Methylarginine: PD, pharmacology
RN **10102-43-9 (Nitric Oxide)**; 15078-28-1 (Nitroprusside); 17035-90-4 (omega-N-Methylarginine); 51-84-3 (Acetylcholine)
CN 0 (Antilipemic Agents); 0 (Drug Combinations); 0 (Enzyme Inhibitors); 0 (Lipids); 0 (Placebos); 0 (Vasodilator Agents)

L54 ANSWER 24 OF 29 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97361830 EMBASE
DOCUMENT NUMBER: 1997361830
TITLE: Prevention of fatty streak formation of 17.beta.-estradiol is not mediated by the production of nitric oxide in apolipoprotein E-deficient mice.
AUTHOR: Elhage R.; Bayard F.; Richard V.; Holvoet P.; Duverger N.; Fievet C.; Arnal J.-F.
CORPORATE SOURCE: Dr. J.-F. Arnal, INSERM U397, Institut L. Bugnard, C.H.U. Rangueil, 1 ave Jean Poulhes, 31054 Toulouse Cedex, France. arnal@rangueil.inserm.fr
SOURCE: Circulation, (1997) 96/9 (3048-3052).
Refs: 42
ISSN: 0009-7322 CODEN: CIRCAZ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Background: Estrogens have atheroprotective properties, the mechanisms of which remain obscure. Estrogens have recently been reported to increase **endothelial NO synthase** expression in castrated animals and to prevent the degradation of NO by decreasing superoxide anion production in cultured endothelial cells. In both cases, increased NO bioavailability would promote vasodilation, inhibit proliferation of the adjacent vascular smooth muscle, reduce platelet aggregation, and inhibit monocyte adhesion to the endothelium and the inflammatory reaction induced by cytokines, all key contributors in the development of atherosclerosis. Methods and Results: In the present work, the respective roles of 17.beta.-estradiol and NO in the development of the atherosclerotic process were investigated in castrated apolipoprotein E- deficient (apo E KO) mice, which spontaneously develop fatty streak lesions within 3 months. N(.omega.)-Nitro-L-**arginine** methyl ester (L-NAME), an NO synthase inhibitor, 50 mg .cntdot. kg-1 .cntdot. d-1, increased arterial blood pressure and decreased cerebellum cGMP content, demonstrating the blockade of NO production, but did not influence the atherogenic process in castrated apo E KO mice. Conclusions: 17.beta.-Estradiol decreased the size of the aortic lesions approximately threefold, and the magnitude of this vasculoprotective effect was not altered by L-NAME. Moreover, L-NAME increased circulating malonyldialdehyde (MDA)-modified LDL, which was not altered by 17.beta.-estradiol, leading to a complete dissociation between circulating MDA-modified LDL and parietal lesions.
CT Medical Descriptors:
*atherosclerosis: DT, drug therapy
*atherosclerosis: PC, prevention
adaptation
animal experiment
animal model
arterial pressure

artery wall
article
bioavailability
cell proliferation
controlled study
enzyme degradation
mouse
nonhuman
priority journal
thrombocyte aggregation
vascular endothelium
vascular smooth muscle
Drug Descriptors:
*apolipoprotein e: CR, drug concentration
*estradiol: DO, drug dose
*estradiol: DT, drug therapy
*estradiol: PD, pharmacology
***nitric oxide**
RN (estradiol) 50-28-2; (nitric oxide) 10102-43-9

L54 ANSWER 25 OF 29 MEDLINE
ACCESSION NUMBER: 96375102 MEDLINE
DOCUMENT NUMBER: 96375102 PubMed ID: 8781483
TITLE: **Increased nitric oxide** synthesis and action preclude choroidal vasoconstriction to hyperoxia in newborn pigs.
AUTHOR: Hardy P; Peri K G; Lahaie I; Varma D R; Chemtob S
CORPORATE SOURCE: Department of Pediatrics, University of Montreal, Quebec, Canada.
SOURCE: CIRCULATION RESEARCH, (1996 Sep) 79 (3) 504-11. Journal code: 0047103. ISSN: 0009-7330.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199610
ENTRY DATE: Entered STN: 19961106
Last Updated on STN: 19961106
Entered Medline: 19961024

AB We tested the hypothesis that hyperoxia does not cause adequate constriction of choroidal vessels of the newborn (1 to 5 days old) pig, resulting in increased O2 delivery to the retina, possibly due to excess production and/or effects of vasodilators such as **nitric oxide** (NO). Hyperoxia (100% O2, 45 minutes) led to a decrease in retinal blood flow (RBF) of both newborn and juvenile (5 to 6 weeks old) pigs and also reduced choroidal blood flow (ChBF) in juvenile but not in newborn pigs; the absence of hyperoxia-induced ChBF response in the newborn was associated with a rise in choroidal O2 delivery. Ibuprofen (prostaglandin G/H synthase inhibitor) and 1,3-dimethyl-2-thiourea (a free radical scavenger) did not modify the choroidal hemodynamic responses to hyperoxia in newborn pigs. However, in newborn animals treated with the NO synthase (NOS) inhibitor NG-nitro-L-**arginine** methyl ester (L-NAME), hyperoxia caused a decrease in blood flow and O2 delivery to the choroid. Consistent with these effects of L-NAME, hyperoxia induced an increase in choroidal cGMP in newborn pigs ventilated with 100% O2 and stimulated nitrite production in isolated choroids exposed to hyperoxia from newborn but not juvenile pigs; these effects were inhibited by NOS

blockers. Also, both constitutive and inducible NOS activities were higher in choroidal tissues from newborn than from juvenile animals. In addition, the vasorelaxant effect of the NO donor sodium nitroprusside in vitro was also greater on choroids from newborn than from juvenile pigs. Finally, L-NAME prevented the hyperoxia-induced increase in peroxidation products in the choroid of newborns. It is concluded that hyperoxia does not lead to a decrease in blood flow and O2 delivery to the choroid of the newborn because of **increased NO** synthesis and effects; since the choroid is the main source of O2 supply to the retina, the present data contribute in providing an explanation for the increased susceptibility of the immature neonate to hyperoxia-induced retinopathy.

CT Check Tags: Animal; Support, Non-U.S. Gov't
Animals, Newborn
Biological Availability
Blood Pressure
*Choroid: BS, blood supply
Choroid: ME, metabolism
Cyclic GMP: BI, biosynthesis
Eye: BS, blood supply
Gases: BL, blood
Heart Rate
*Hyperoxia: PP, physiopathology
Intraocular Pressure
***Nitric Oxide: BI, biosynthesis**
***Nitric Oxide: PH, physiology**
Nitrites: ME, metabolism
Oxygen: BL, blood
Regional Blood Flow
Retinal Vessels: PP, physiopathology
Swine
Vascular Resistance
*Vasoconstriction

RN **10102-43-9 (Nitric Oxide)**; 7665-99-8 (Cyclic GMP); 7782-44-7 (Oxygen)

CN 0 (Gases); 0 (Nitrites)

L54 ANSWER 26 OF 29 MEDLINE

ACCESSION NUMBER: 94052005 MEDLINE
DOCUMENT NUMBER: 94052005 PubMed ID: 7694272
TITLE: Absorption of recombinant human granulocyte colony-stimulating factor (rhG-CSF) from rat nasal mucosa.
AUTHOR: Machida M; Sano K; Arakawa M; Hayashi M; Awazu S
CORPORATE SOURCE: Formulation Technology Laboratory, Chugai Pharmaceutical Co., Ltd., Tokyo, Japan.
SOURCE: PHARMACEUTICAL RESEARCH, (1993 Sep) 10 (9) 1372-7. Journal code: 8406521. ISSN: 0724-8741.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199312
ENTRY DATE: Entered STN: 19940117
Last Updated on STN: 19960129
Entered Medline: 19931209

AB Nasal absorption of recombinant human granulocyte colony-stimulating factor (rhG-CSF) was examined in the rat. The relative bioavailability of rhG-CSF for subcutaneous administration was approximately 2%, as evaluated

from the immunologically active rhG-CSF concentration in rat plasma and the area under the curve (AUC) of the plasma rhG-CSF concentration versus time for 8 hr. Pharmacological availability relative to subcutaneous administration was determined from the increase in total blood leukocyte numbers. The pharmacological availability was 5-10%, determined from the AUC for the increased ratio of total leukocyte numbers versus time for 48 hr; it was slightly dependent on the pH and the osmotic pressure of the dosing solution. Accordingly, the plasma concentration of rhG-CSF did not always reflect its pharmacological effects. Relative bioavailability and pharmacological availability were increased about 23 times and 3 times, respectively, by polyoxyethylene 9-lauryl ether (Laureth-9), but **no increase** in availability occurred with sodium glycocholate. The increase in total leukocyte numbers was maintained during multiple rhG-CSF dosing, and the addition of Laureth-9 further increased the pharmacological effects of this agent. This study indicates that nasal administration of rhG-CSF is an effective parenteral administration route.

CT Check Tags: Animal; Comparative Study; Male
Absorption
Administration, Intranasal
Biological Availability
Excipients
Granulocyte Colony-Stimulating Factor: CF, cerebrospinal fluid
*Granulocyte Colony-Stimulating Factor: PK, pharmacokinetics
Granulocyte Colony-Stimulating Factor: PD, pharmacology
Injections, Intravenous
Injections, Subcutaneous
Leukocyte Count: DE, drug effects
*Nasal Mucosa: ME, metabolism
Rats
Rats, Sprague-Dawley
Recombinant Proteins: CF, cerebrospinal fluid
Recombinant Proteins: PK, pharmacokinetics
Recombinant Proteins: PD, pharmacology
RN 143011-72-7 (Granulocyte Colony-Stimulating Factor)
CN 0 (Excipients); 0 (Recombinant Proteins)

L54 ANSWER 27 OF 29 MEDLINE
ACCESSION NUMBER: 93277578 MEDLINE
DOCUMENT NUMBER: 93277578 PubMed ID: 8503929
TITLE: Availability of **tetrahydrobiopterin** is not a factor in the inability to detect **nitric oxide** production by human macrophages.
AUTHOR: Sakai N; Milstien S
CORPORATE SOURCE: Laboratory of Neurochemistry, National Institute of Mental Health National Institutes of Health, Bethesda, MD 20892.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1993 May 28) 193 (1) 378-83.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199307
ENTRY DATE: Entered STN: 19930716
Last Updated on STN: 19930716
Entered Medline: 19930701

AB Human macrophages, in contrast to murine macrophages, do not produce **nitric oxide** after stimulation with cytokines. This failure has been attributed to the known lack of production by human macrophages of **tetrahydrobiopterin**, an essential cofactor for **nitric oxide** synthase. **Increasing** intracellular levels of **tetrahydrobiopterin** in cytokine-stimulated murine cells results in an increase in nitrite production. However, this treatment does not result in any detectable accumulation of nitrite by stimulated human monocyte-derived macrophages. Thus, the inability of these cells to produce **nitric oxide** appears to be unrelated to a lack of **tetrahydrobiopterin** and suggests that proper in vitro conditions may not yet have been discovered that permit **nitric oxide** synthesis by activated human macrophages.

CT Check Tags: Human; Support, U.S. Gov't, P.H.S.

Biological Availability
*Biopterin: AA, analogs & derivatives
Biopterin: ME, metabolism
Biopterin: PD, pharmacology
Cell Line
Cells, Cultured
Interferon Type II: PD, pharmacology
Macrophages: DE, drug effects
*Macrophages: ME, metabolism
***Nitric Oxide: ME, metabolism**
Recombinant Proteins: PD, pharmacology
Tumor Necrosis Factor: PD, pharmacology

RN **10102-43-9 (Nitric Oxide); 17528-72-2 (5,6,7,8-tetrahydrobiopterin);** 22150-76-1 (Biopterin); 82115-62-6 (Interferon Type II)

CN 0 (Recombinant Proteins); 0 (Tumor Necrosis Factor)

L54 ANSWER 28 OF 29 MEDLINE

ACCESSION NUMBER: 90297317 MEDLINE
DOCUMENT NUMBER: 90297317 PubMed ID: 2360675
TITLE: Myocardial and systemic oxygenation during severe hypoxemia in ventilated lambs.
AUTHOR: Bernstein D; Teitel D F
CORPORATE SOURCE: Cardiovascular Research Institute, University of California, San Francisco 94143.
CONTRACT NUMBER: HL-07143 (NHLBI)
HL-23681 (NHLBI)
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, (1990 Jun) 258 (6 Pt 2) H1856-64.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199008
ENTRY DATE: Entered STN: 19900907
Last Updated on STN: 19900907
Entered Medline: 19900802

AB We studied the interrelationships among myocardial oxygenation, cardiac output, and systemic oxygenation during acute progressive hypoxemia in the paralyzed and mechanically ventilated lamb. Fractional inspired concentration of oxygen was reduced in five steps to a minimum of 0.05,

decreasing arterial oxygen content (CaO2) from 10.9 +/- 2.4 to 2.8 +/- 0.5 ml/dl. Heart rate and stroke volume did not change at any step so that systemic oxygen transport decreased with CaO2. Systemic oxygen consumption fell at CaO2 less than 6 ml/dl. Left ventricular blood flow at maximal hypoxemia increased 277% (249 +/- 27 to 938 +/- 118 ml.min-1.100 g-1) so that left ventricular oxygen delivery and oxygen consumption were maintained. Evidence of anaerobic metabolism occurred when CaO2 was less than four (increase in arterial lactate and hypoxanthine), whereas at this level there was no evidence of inadequate myocardial oxygenation as determined by normal subepicardial: subendocardial blood flow and absence of net lactate production, although coronary sinus PO2 decreased. Although myocardial, **cerebral**, and adrenal blood flows **increased** , there was **no** redistribution of blood flow away from the viscera and skin.

CT Check Tags: Animal; Comparative Study; Support, U.S. Gov't, P.H.S.
Animals, Newborn: GD, growth & development
Animals, Newborn: ME, metabolism
*Anoxemia: ME, metabolism
Biological Availability
*Myocardium: ME, metabolism
Oxygen: PK, pharmacokinetics
*Oxygen Consumption
Regional Blood Flow
*Respiration, Artificial
Sheep

RN 7782-44-7 (Oxygen)

L54 ANSWER 29 OF 29 MEDLINE
ACCESSION NUMBER: 84210160 MEDLINE
DOCUMENT NUMBER: 84210160 PubMed ID: 6539288
TITLE: Aluminium concentrations in the **brain** and bone of rats fed citric acid, aluminium citrate or aluminium hydroxide.
AUTHOR: Slanina P; Falkeborn Y; Frech W; Cedergren A
SOURCE: FOOD AND CHEMICAL TOXICOLOGY, (1984 May) 22 (5) 391-7. Journal code: 8207483. ISSN: 0278-6915.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198407
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19970203
Entered Medline: 19840706

AB Male Sprague-Dawley rats were treated daily by gastric intubation (6 days/wk) with 100 mg aluminium/kg body weight in the form of aluminium hydroxide (9 wk) or aluminium citrate (4 wk), with citric acid (4 wk) or with tap-water (control, 9 wk). Young adult and aged Wistar rats were treated with 100 mg aluminium/kg body weight as aluminium hydroxide or with carboxymethylcellulose (vehicle controls). The **cerebral** cortex, hippocampus, cerebellum and samples of bone from each rat were analysed for aluminium, after digestion with nitric acid, using graphite furnace atomic absorption spectroscopy. The mean aluminium concentrations detected in the control Sprague-Dawley rats were 0.013-0.022 microgram/g wet weight in the various **brain** regions and 0.355 microgram/g in the bone. **No** significant **increase** in tissue aluminium concentrations was observed in Sprague-Dawley or Wistar rats after

treatment with aluminium hydroxide. However the rats treated with aluminium citrate showed significantly increased concentrations of aluminium in all the **brain** regions studied (0.057-0.121 microgram Al/g) and in the bone (12.9 micrograms Al/g). Elevated aluminium concentrations in the **cerebral** cortex and bone were also observed in the animals fed citric acid suggesting possible absorption of the citrate chelate presumably formed with the traces of aluminium present in the diet.

CT Check Tags: Animal; Female; Male
*Aluminum: ME, metabolism
*Aluminum Hydroxide: ME, metabolism
Biological Availability
Bone and Bones: DE, drug effects
*Bone and Bones: ME, metabolism
Brain: DE, drug effects
***Brain: ME, metabolism**
*Citrates: ME, metabolism
*Citrates: PD, pharmacology
Citric Acid
Intestinal Absorption: DE, drug effects
Rats
Rats, Inbred Strains

RN 21645-51-2 (Aluminum Hydroxide); 7429-90-5 (Aluminum); 77-92-9 (Citric Acid)

CN 0 (Citrates)